Annex to:

EFSA NDA Panel, 2022. Scientific Opinion on the Tolerable Upper Intake Level for dietary sugars. EFSA Journal 2022;20(2):7074. doi:10.2903/j.efsa.2022.7074

Annex M – Statistical analysis of evidence from observational studies identified in the published scientific literature as preparatory work for the setting of a Tolerable Upper Intake Level for dietary sugars

Summary

The current report was drafted based on the Protocol (and related amendments) for the scientific opinion on the Tolerable Upper Intake Limit for dietary sugars by the NDA Panel (from this point forwards referred to as 'the Protocol') and the actual analysis carried out consistently with the plan.

The overall objective of this analysis was to contribute to answer sub-question 4 from the Protocol 'What is the relationship between the intake of (total/added/free) sugars and metabolic diseases (disease endpoints and other endpoints) in the target population?', with a focus on characterising quantitatively the dose–response relationships between dietary sugars intake and selected health outcomes in the healthy population based on evidence from observational studies as identified in the scientific published literature.

Several systematic reviews were conducted in-house to characterise such relationships; the Protocol and Section 7 (and related Appendices and Annexes) in the scientific opinion describe the planning, conduction and outcome of the systematic review steps (eligibility criteria, literature searches, screening for relevance, risk of bias assessment) preliminary to the meta-analyses and dose–response analyses included in the current report; as such they should be considered as key complementary information for the interpretation of the analysis results.

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1. Evidence synthesis

Five types of exposure and seven metabolic diseases were identified in the scientific opinion based on the evidence mapping resulting from the study selection process. A complete list of all selected relationships, which includes both the current subset and those that were assessed only narratively, is presented in Figure 6 and Table 12 of the scientific opinion (Section 8.1.3). Effect estimates from eligible observational studies (prospective cohorts and nested case–cohorts) that met the criteria specified in Section 2.1. of this Annex were displayed in forest plots and used, when possible, to characterise dose–response relationships. The methods applied are in line with those outlined in the Cochrane Handbook for Systematic Reviews (Higgins et al., 2021).

2. Methods

2.1. Criteria under which study data were quantitatively synthesised

Effect estimates from eligible individual studies were displayed in forest plots whenever a minimum of three study-specific estimates were available. Pooling and modelling were considered only when a minimum of five study-specific estimates were available (four relationships explored in dose–response analyses on aggregated data).

Effect estimates from eligible individual studies from small and heterogeneous bodies of evidence (less than three study-specific estimates) were discussed narratively (including original individual-data dose–response analyses); no forest plots were produced and no modelling was possible/deemed appropriate (with the only exception of risk of gout and its selected exposures).

The threshold of three studies was chosen as no method has been developed so far that allows a satisfactory estimation of heterogeneity between two studies (Gonnermann et al., 2015); the threshold of five studies was considered as the minimum to be able to perform subgroup analyses and dose–response analyses, considering that the number of category-specific non-referent effect estimates varies greatly across studies (ranging from a minimum of one to typically four when quintiles are calculated to categorise the exposure).

The expected high heterogeneity across the studies identified to characterise the associations between the intake of dietary sugars and metabolic diseases was taken into account in meta-analyses and dose–response analyses applying a random-effects model (Borenstein et al., 2010); such a model assumes that the true effects are normally distributed around a pooled weighted mean (or around the linear predictor for models) and allows for residual heterogeneity among responses not otherwise characterised by subgroups analyses (or not modelled by the explanatory variables included in multivariable models).

All statistical analyses were performed with Stata version 15.1 (StatCorp, 2015). All estimates were presented with 95% confidence intervals (CI) and all analyses carried out at the level of statistical significance of 0.05.

2.2. Summary effect measures

For most exposure–endpoint relationships the effect estimates extracted from the original individual studies were relative risks (RRs) expressed in different metrics, consistently with the type of outcome (dichotomous), original study design and analytical approach.

The only exceptions were effect estimates for continuous outcomes such as measures of body weight, body mass index, body fat, waist circumference and abdominal fat body mass index, body fat, which were extracted as beta coefficients from multivariable models with their 95% CI and included as such in the forest plots (no standardisation of measures was deemed possible due to the very high variability in metrics across studies).

All effect estimates were extracted following a 'contrast-based' approach (not from original summary data) and considering all relevant multivariable models reported in the original papers with different degrees of adjustment for potential confounders (crude or minimally adjusted, intermediately adjusted, fully adjusted); as the impact of covariates such as energy intake and body mass index (BMI) was considered of particular interest models were also characterised depending on whether they were

adjusted for these variables or not.

When possible, summary RRs (with 95% CI) were estimated by pooling the study-specific hazard ratios, odds ratios, or risk ratios, assuming a random-effects model and applying the inverse-variance method. Hazard ratios, odds ratios and risk ratios were displayed and/or combined ignoring the differences in metrics. This was considered appropriate because of the study designs included in the body of evidence (cohort studies or case–cohort studies). The different metrics were reported in a specific column of the forest plots.

Individual-study RRs estimates were treated depending on how they were subsequently used:

- Qualitative assessment of effects across studies (descriptive forest plots with no pooling): the estimates were included as reported in the original papers, either in the form of RRs per unit increase in intake or as RRs per category of intake.
- Quantitative assessment of effects across studies and dose–response meta-analysis (meta-analytic forest plots with pooled effect estimation): the RRs per unit increase in intake were estimated from the category-specific RRs reported in the original papers applying a two-stage approach (Orsini et al., 2012) and assuming a linear trend; the single estimate per study obtained in this way could be pooled and used in subgroup analyses. However, the original categorical RRs were retained for the one-stage dose–response meta-analysis, as requested by the approach.

An alternative to the estimation of a RR per unit increase when a single estimate per study is needed is the high-versus-low approach, where only the highest contrast from each study is included in the analysis (the effect of the highest category of intake when compared with the lowest category). This approach was applied in limited cases for descriptive purposes only; in fact, part of the information about the shape of the dose–response is lost and the power of detecting an association may considerably decrease. In addition, in a high-versus-low analysis, the highest and the lowest category are usually associated to a different exposure value in the studies included in the meta-analysis.

2.3. Unit of analysis issues

Published dose–response data are typically reported as a series of category-specific RRs, with one category serving as the common referent group. Assuming zero correlation among a series of log RRs estimated using a common referent group leads to a biased estimate for the variance of the trend; the Greenland and Longnecker's method (Greenland and Longnecker, 1992) was applied in the dose–response analyses to approximate these correlations and incorporate them into the estimation of the linear trend using generalised least-squares model.

When a study reported sex-specific effects they were treated as independent estimates; this was considered informative for the qualitative assessments, while it increased the number of available points to be included in the dose–response analyses. The possible correlation between same-study estimates might have spuriously increased the pooled estimates precision when these were meta-analysed.

2.4. Data checking and management

For each variable extracted, the proportion of missing observations was assessed, and range checks carried out to ensure that all values were plausible. The distributions of continuous variables were explored graphically, and the frequency distributions of categorical variables tabulated. Key variables were cross-tabulated or scattered against each other to check for consistency. Effect estimates were double checked against original publications whenever deemed necessary, and unit conversions of all included sugars intake values carried out when requested.

When meta-analysed, RRs with their standard errors were log-transformed and results were reported back to the original scale as RRs with their 95% CIs. The plotted CIs were re-estimated from the standard errors; in a few cases they did not correspond to the original figures from the papers. Since CIs are symmetric around the point estimate on the logarithmic scale, the discrepancies were attributed to potential reporting mistakes by the original authors.

2.5. Dealing with missing data

Studies were included in forest plots only when the effect estimates were reported with an estimate of their sampling error, either expressed as 95% confidence interval, standard error, or as a p-value from a hypothesis test.

In the descriptive forest plots the number of participants in analysis was reported as number of person years when not available; age was collected as either mean, median or range and included as such in the plots to maximise the information available; exposure was reported as either mean, median or range of intake.

The number of cases and the number of person years by intake category were needed to approximate the correlation across RRs from the same study in the dose–response meta-analyses; when either one of the two was missing it was possible to estimate an approximate distribution using the total number of cases/person years applying the Aune method (Aune et al., 2012).

During data extraction, authors were contacted for additional information, when appropriate.

2.6. Assessment of heterogeneity

Statistical heterogeneity was tested using the chi-squared (χ^2) test (Cochran's Q test) and was quantified by calculating the I^2 statistic. I^2 provides an estimate of the proportion of between-study variability that is attributed to heterogeneity rather than chance (Higgins and Thompson, 2002). As such it does not represent an absolute estimate of the heterogeneity that occurs in a body of evidence.

2.7. Meta-analyses: forest plots and pooled estimates

Forest plots display effect estimates and CIs from individual studies and may or may not include pooled estimates based on a weighted mean across them. For the purposes of the current analyses two types of plots were produced using the *metan* Stata module (Fisher et al. 2006):

- Plots of multiple effect estimates from each study, which included results (either continuous or categorical) from all multivariable models with increasing level of adjustment and sorted by increasing exposure levels: no pooling carried out, descriptive purpose.
- Plots of one effect estimate per study (per unit of increase in intake), including results only from most adjusted multivariable models: pooling carried out, meta-analytic purpose (overall pooled estimates and subgroup analyses estimates were part of dose–response analyses and retained for evidence integration and uncertainty analysis).

In the former type of plot, information was displayed and sorted depending on the specific purpose:

- To compare general characteristics across studies and assess how those would be associated with effect estimates: by including contextual and methodological information along with estimates from one model per study.
- To get a visual picture of how model strategy impacted on effect estimates (i.e. potential confounders included in the original analyses, mediators, and so on): by including estimates from all models and mapping their covariates.

Independently of the type, each study was represented by a block at the point estimate of exposure effect with a horizontal line extending either side of the block. The area of the block indicated the weight assigned to that study while the horizontal line depicted the 95% CI.

When applicable, random-effects meta-analyses of individual-study estimates were carried out using the DerSimonian and Laird approach (DerSimonian and Laird, 1986), which encompasses both variability due to chance (i.e. the within-study variance component in the denominator of the individual-study weight) and variability due to heterogeneity (i.e. the between-study variance component added in the denominator of the individual-study weight; tau-squared statistic). Tau-squared ($\tau 2$) was estimated using the DerSimonian–Laird method (DerSimonian and Laird, 1986); Wald-type 95% CIs were estimated for all pooled estimates.

2.8. Dose–response models

Parametric dose–response models were estimated based on aggregated data using the *drmeta* Stata

module (Orsini, 2019). Random-effects models were fitted via restricted maximum likelihood using a one-stage approach (Crippa et al., 2019) for the dose–response meta-analyses and a two-stage approach (Liu et al., 2009; Orsini et al., 2012) to estimate individual-study pooled effects (linear trends) across exposure categories. In the one-stage (or 'pool-first') approach study-specific data are combined first and then one summary dose–response model is fitted.

Effect measures included odds ratios, risk ratios and hazard ratios from most adjusted multivariable models; relevant descriptive statistics (number of cases and person years by intake category) were used to reconstruct their covariances, which were used to define the study-specific weights in the mixed models.

Assignment of exposure scores (single values representative of exposure in each category that served as independent variable) was carried out according to the Il'yasova approach (Il'yasova et al., 2005). Whenever reported, the mean or median intake by category was assigned to the corresponding RR. The midpoint was calculated for studies that only reported a range of intake by category; when the intake range was open ended, the upper boundary was estimated adding the width of the second-highest category to its lower boundary. When the width of the second-highest category was 0, the lower boundary value was multiplied by a constant of 1.2. Depending on data availability and type of related approach the uncertainty in the assignment increases by moving from the first approach to the fourth one.

Both linear and non-linear dose–response relationships were investigated. Potential non-linear dose–response relationships were examined using restricted cubic splines (RCS) with three knots at 10%, 50% and 90% percentiles of the intake distribution, which were combined in the one-stage model. The three knots' locations chosen as a starting point for the non-linear shape were based on Harrell's recommended percentiles (Harrell, 2001).

Relative risk was modelled with RCS to ensure more flexibility, as no *a priori* assumptions on the dose–response curve shape were required and non-linear non-monotonic functional relationships (e.g. J-shaped curves) could be accommodated using only two parameters. A Wald-type test was applied to detect departure from a simpler linear function.

Hypothesis testing, identification of statistical heterogeneity, predictions and graphical presentation of the pooled dose–response curve were carried out according to the methods described in Orsini et al. (2012) and Crippa et al. (2019).

Outliers and influential studies were detected and tests for normality and homoscedasticity carried out to check for model assumptions (e.g. normality of the random effects).

The maximised log-likelihood, the Akaike Information Criteria (AIC), the deviance and R^2 (coefficient of determination) were used to compare alternative models and assess their goodness-of-fit (Discacciati et al., 2017); visual inspection of decorrelated residuals plotted against the exposure was also applied to evaluate how the pooled dose–response curves fitted the data according to the exposure levels.

2.8.1. Dose–response moderators

Several factors potentially influencing the dose–response relationships were identified *a priori* both from the literature and by the Panel.

Subgroup analyses were performed to characterise methodological sources of heterogeneity and to evaluate the influence of contextual sources of heterogeneity as potential effect modifiers.

Contextual sources of heterogeneity included:

- Age: 2 categories, depending on age range and median (e.g. <55 years, old, ≥55 years old)
- Sex: Females, Males, Mixed
- Study location: USA, Europe, Asia.

Methodological sources of heterogeneity included:

- Follow-up duration: two categories, depending on time range and median (e.g. ≤10 years, >10 years).

- Type of referent exposure category: Non-consumers, Other than non-consumers.
- Risk of bias tier: tier 1, tier 2, tier 3.

The subgroup analyses were run on the linear RRs per unit increase in intake (250 mL/day) to assess pooled estimates by subgroup based on one estimate per study, when of interest.

2.8.2. Dose–response results

Linear and non-linear dose–response relationships between dietary sugar intakes and risk of disease were plotted on the same graph to allow for a direct comparison of the shapes. Individual-study RR estimates from most adjusted models were represented by circles proportionate to their weight in the mixed models. An orange line represented the linear model and a black line represented the non-linear model, respectively. Dotted lines represented 95% CIs of the non-linear model. A red dotted line was used to show the reference value (RR = 1, corresponding to a level of intake of 0 mL/day).

Predicted average RRs (and 95% CIs) estimated per 250 mL/d increase in intake from linear curves and at 250 mL/day of intake from non-linear curves were included in the plot, together with p-values from tests for linearity and non-linearity. A full set of RR values by increasing intakes from their observed range was predicted from the dose–response models for each relationship.

2.9. Addressing risk of bias in the analysis

The outcome of the risk of bias assessment (individual dimensions and overall assessment) was used to evaluate whether heterogeneity of results could be attributed to differences in internal validity across individual studies. Subgroup analyses and/or sensitivity analyses were carried out based on the overall risk of bias (RoB) rating as expressed by different tiers of reliability (tiers 1, 2 and 3), while individual bias dimensions were discussed together with other potential sources of heterogeneity reported in forest plots.

2.10. Sensitivity analyses

Sensitivity analyses were carried out to evaluate whether the findings were robust to the assumptions made in the systematic review protocols and the analyses.

There were several choices/issues provisionally identified that could potentially be tested in sensitivity analyses by comparing the results obtained with alternative input parameters to those from the default model or by restricting to specific subsets.

The following analyses were considered:

- On studies with characteristics departing from the rest of the body of evidence (different outcome and/or exposure characterisation).
- On studies for which the original analytical approach could impact on the outcome interpretation.
- On alternative methods for assigning the exposure scores needed to perform the dose–response meta-analyses.
- On alternative choices about the number and location of knots when modelling the dose–response curve applying RCS.

2.11. Publication bias

Several systematic reviews of empirical studies have found that studies with statistically significant ($p < 0.05$) or positive results are more likely to be published than those with non-significant or negative results and tend to be published earlier.

Publication bias assessment was planned for the exposure–endpoints relationships for which it was possible to carry out a dose–response characterisation [SSBs-T2DM, FJs-T2DM, SSBs-HTN, SSBs-cardiovascular diseases (CVD)]; it was assessed by visual inspection of the funnel plot (Sterne et al., 2011) and by performing Egger's test for funnel plot asymmetry (Egger et al., 1997) on the RRs per

unit increase in intake estimated from the category-specific RRs of the prospective cohorts included in the meta-analyses. Contours of statistical significance were superimposed on the funnel plot to help evaluate potential small-study effects.

Funnel plots investigate the association between study size and effect size; indications of funnel plot asymmetry were interpreted considering also possible alternative explanations to publication bias (Sterne et al., 2011). Egger's test was performed to generate a linear regression of the RRs on their standard errors, weighted by 1/(variance of the summary estimate); it is a test with some limitations, especially when the number of studies is small and the effect estimate dichotomous.

Publication bias was assessed using Egger's test and funnel plots on the same-study-specific linear RRs used in the subgroup analyses. Enhanced versions (Peters et al., 2008) of the funnel plots included contour lines corresponding to perceived 'milestones' of statistical significance ($p = 0.01$, 0.05, 0.1, etc.) to help to differentiate asymmetry due to publication bias from that due to other factors.

3. Results

Results are reported following the same structure used in the scientific opinion; they include a subset of all the observational evidence assessed in the opinion and are related to the exposure–endpoint relationships for which it was meaningful to produce forest plots of the effect estimates across studies. Dose–response meta-analyses were used when possible and carried out for four of these relationships.

The general characteristics of the eligible observational studies, the outcome of their RoB assessment and their effect estimates are summarised in evidence tables, heatmap tables and forest plots, respectively, in appendices to the scientific opinion; these are specified by endpoint in the following sections for immediate reference.

3.1. Risk of obesity

The characteristics of the eligible observational studies for this endpoint are summarised in evidence tables in **Annex J** to the scientific opinion following the same order by exposure.

The outcome of the RoB assessment of the same studies is summarised in heatmap tables in **Appendix L** to the scientific opinion following the same order by exposure within the same endpoint.

Forest plots to visualise and interpret the effect estimates across studies were produced for the following exposures: sugar-sweetened beverages (SSBs), fruit juices (FJs). They are reported in **Appendix K** to the scientific opinion (**Figures K1–K5**).

3.2. Risk of type 2 diabetes mellitus

The characteristics of the eligible observational studies for this endpoint are summarised in evidence tables in **Annex J** to the scientific opinion following the same order by exposure.

The outcome of the RoB assessment of the same studies is summarised in heatmap tables in **Appendix L** to the scientific opinion following the same order by exposure within the same endpoint.

Forest plots to visualise and interpret the effect estimates across studies were produced for the following exposures: total sugars, added (and free) sugars (free glucose, total sucrose), fructose, SSBs, FJs. They are reported in **Appendix K** to the scientific opinion (**Figures K6–K11**).

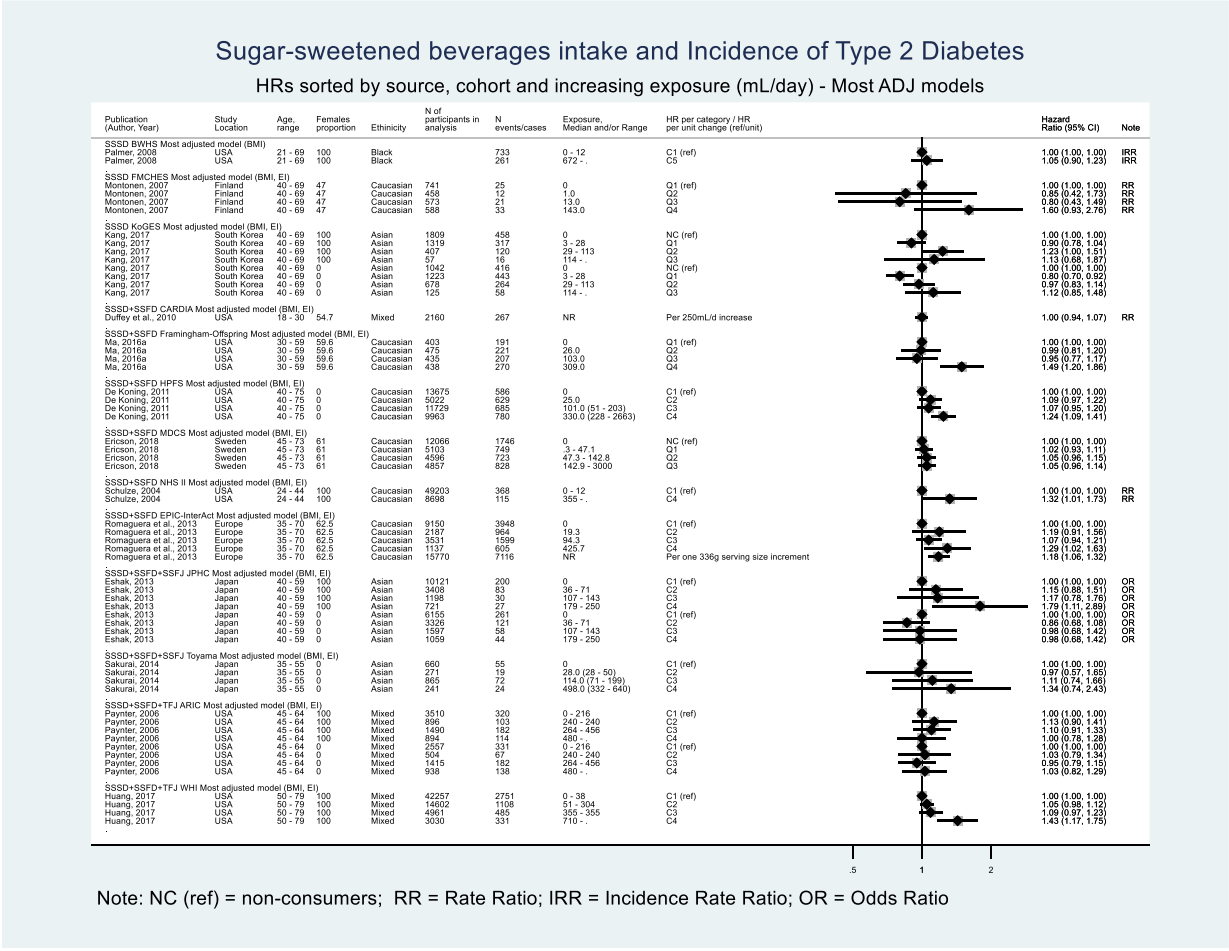
It was possible to carry out dose–response meta-analyses for the relationships between consumption of SSBs and risk of type 2 diabetes mellitus (T2DM) and between consumption of FJs and risk of T2DM.

3.2.1. Sugar-sweetened beverages

3.2.1.1. Forest plots and pooled estimates

The relationship between the intake of SSBs and incidence of T2DM was investigated in 14 studies, of which 13 were PCs and one was a prospective case-cohort (PCC) study. These include three PCs in which the endpoint was high fasting glucose (>100 or 110 mg/dL, depending on the study) or the use of hypoglycaemic medications [Coronary Artery Risk Development in Young Adults study (CARDIA), Korean Genome and Epidemiology Study (KoGES), Tehran Lipid and Glucose Study (TLGS)], and one PC

that investigated incidence of prediabetes and incidence of T2DM as a composite endpoint (Framingham Offspring).

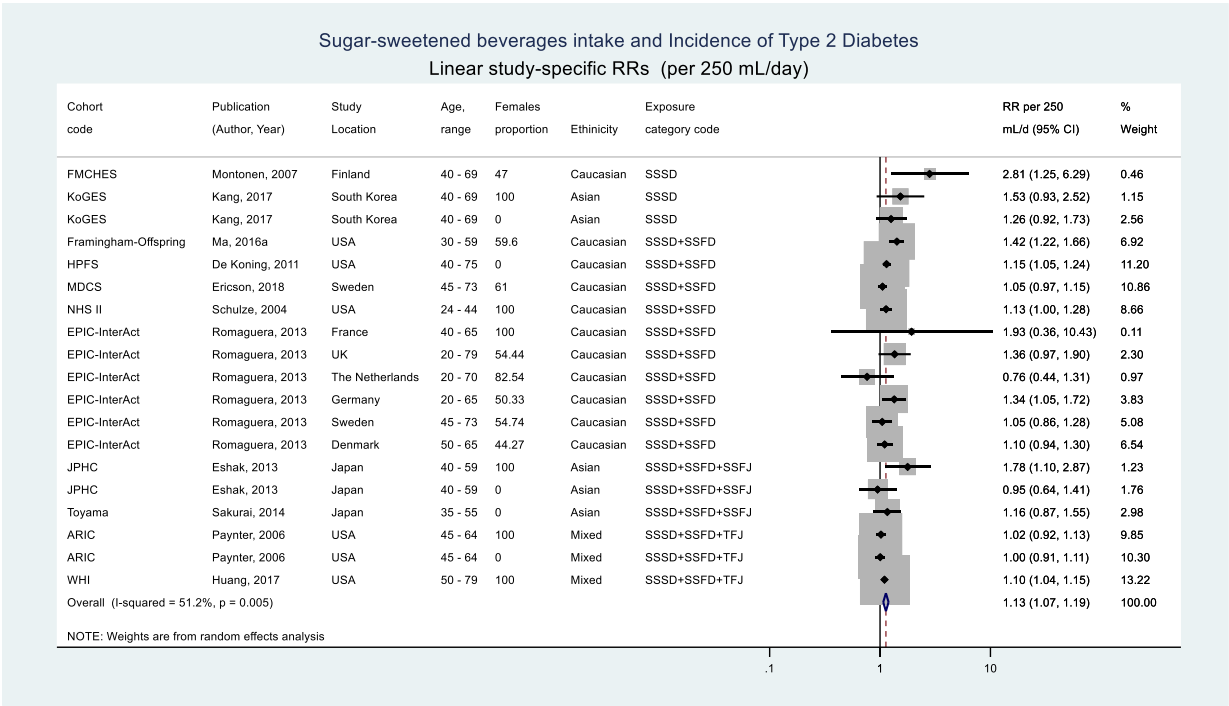


Individual-study effect estimates from most adjusted models are sorted by source, cohort and increasing exposure.

Figure 1: Forest plot – prospective associations of SSBs intake with incidence of T2DM

3.2.1.2. Dose–response model

Fifty-five non-referent RRs from 19 study-specific analyses (11 PCs: 291,411 subjects and 24,503 cases) were eligible for inclusion in the dose–response analysis (I^2 = 51%; p = 0.001). The TLGS (number of cases not reported), BWHS (model diagnostics), and CARDIA (RR already provided per unit increase) cohorts were excluded. Upon request for additional data from the authors of the EPIC-InterAct study, individual country-specific cohort risk estimates were included in the dose–response analysis. Main characteristics of included studies are summarised in Table A.1 (Appendix A).

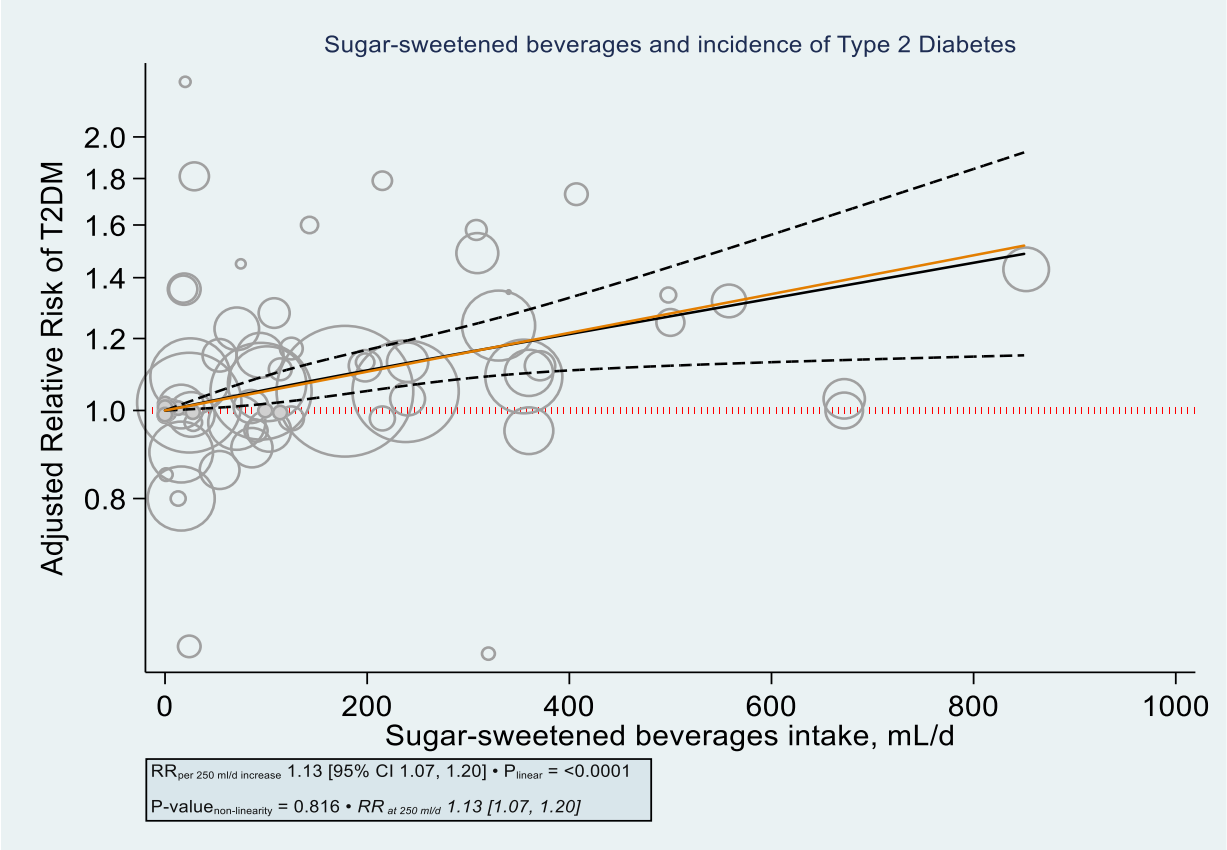


Individual-study RRs estimated per 250 mL/day increase in SSBs consumption are sorted by cohort; a pooled risk estimate is provided with its 95% confidence interval and between-study heterogeneity is quantified using the I^2 statistics and tested using the Cochrane Q statistics (p-value reported).

Figure 2: Forest plot – prospective associations of SSBs intake with incidence of T2DM included in the dose–response meta-analysis

Main results

The predicted pooled RR of T2DM for an increase in SSBs intake of 250 ml/d was 1.134 (95% CI: 1.07, 1.20) assuming a linear dose–response relationship (p for linear trend < 0.0001), while it was 1.13 (95% CI: 1.07, 1.20) at 250 ml/d in the non-linear model (RCS with three knots at fixed percentiles, 10%, 50%, and 90%, of the distribution; p for non-linearity = 0.816) (Figure 3). Exposure scores were assigned mostly as mean/median and midrange values, with a couple of points in the highest boundary of the exposure range bearing the highest uncertainty (Figure C.1, Appendix C). The decorrelated residuals-versus-exposure plot assessing the goodness-of-fit of the model is reported in Appendix B (Figure B.1). Predicted RRs (with their 95% CI) by relevant intakes from both the linear and the non-linear model are reported in Table G.1 (Appendix G).



Individual-study relative risk estimates from most adjusted models are plotted on the log scale and are represented by circles that are proportionate to their weight in the mixed model. The orange line represents the linear, and the black line represents the non-linear model, respectively, while the dotted red line is the reference (RR = 1). Dashed lines represent the 95% CI for the spline model. The value of 0 mL/day intake served as reference.

Figure 3: Linear and non-linear dose–response relationships between sugars-sweetened beverages intake and incidence of type 2 diabetes

Subgroup analyses, sensitivity analyses and publication bias

All subgroup results were interpreted only qualitatively, and summary estimates compared by visual inspection (I^2 range: 0–77%). The stratified analyses did not identify clear sources of heterogeneity: there was a suggestion that the risk was higher in subjects younger than 55 years old; in Asian populations; in cohorts with longer follow-up; in RoB tier 2 studies (Table 1).

Table 1: Subgroup analyses results on RR of T2DM per unit increase in SSBs are summarised below and displayed in forest plots in Appendix D. I^2 is the estimated proportion of variance due to heterogeneity in each subgroup; the p-value of the test for heterogeneity based on Cochran's Q statistic is reported in the last column

	Subgroups	N studies	N subjects	RR	95% CI		I^2	p
All	**Adults**	19	291411	1.13	1.07	1.19	51%	0.005
Age	**Adults < 55 years**	9	130947	1.24	1.10	1.40	40%	0.104
	Adults ≥ 55 years	10	160464	1.08	1.03	1.14	37%	0.111
Sex	**Females**	5	181929	1.11	1.02	1.21	49%	0.098
	Males	5	63045	1.09	1.00	1.19	29%	0.227
	Mixed	9	46437	1.19	1.05	1.36	64%	0.005

Study location	**United States**	6	210377	1.11	1.04	1.20	71%	0.004
	Europe	8	44752	1.14	1.01	1.28	44%	0.083
	Asia	5	36282	1.25	1.04	1.50	17%	0.306
Follow-up time	**≤10 years**	9	204585	1.09	1.02	1.15	33%	0.152
	> 10 years	10	86826	1.18	1.07	1.30	59%	0.009
Exposure referent category	**Referent other than non-consumer (NC)**	16	258129	1.13	1.07	1.21	55%	0.004
	Non-consumers as referent	3	33282	1.15	0.96	1.37	36%	0.212
Tier	**Tier 1**	5	56315	1.13	1.01	1.26	77%	0.002
	Tier 2	11	140556	1.19	1.06	1.34	39%	0.092
	Tier 3	3	94540	1.09	1.04	1.14	0%	0.485

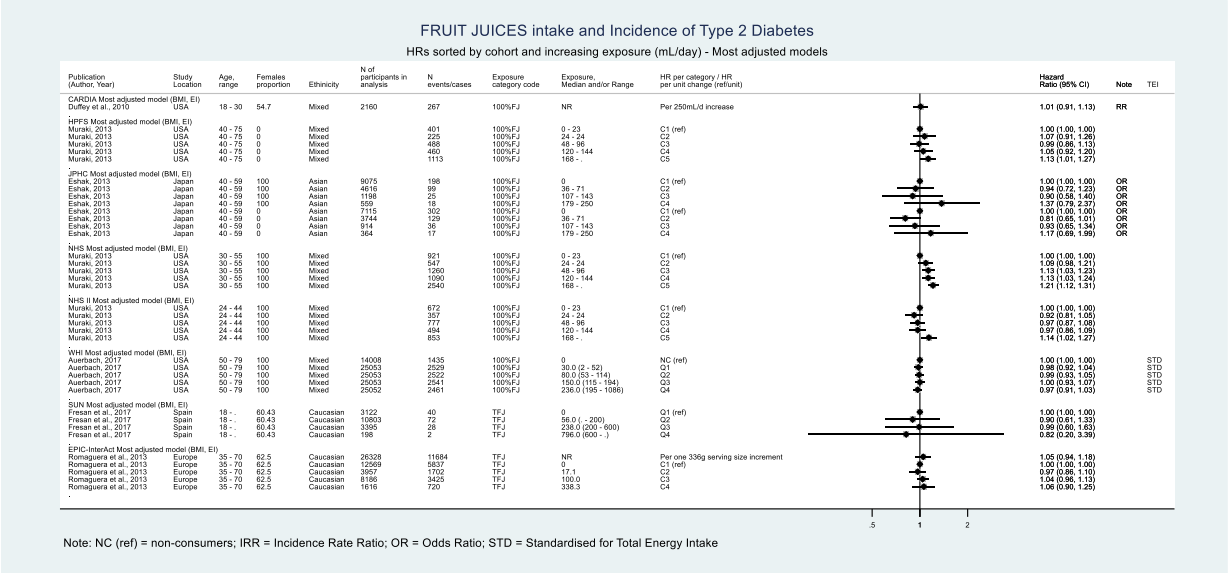
A sensitivity analysis excluding RoB tier 3 studies confirmed no evidence of departure from linearity (p = 0.295) and showed higher RRs estimates [(1.15; 95% CI: 1.06, 1.24), (1.19; 95% CI: 1.09, 1.29)], narrower exposure range and improved fitting (Figure E.1, Appendix E). A sensitivity analysis excluding a study that defined the outcome as either T2DM or prediabetes (Ma et al., 2016) showed very weak evidence of departure from linearity (p = 0.114) and decreased RRs estimates [(1.09; 95% CI: 1.06, 1.13), (1.14; 95% CI: 1.08, 1.21)] (Figure E.2, Appendix E).

The funnel plot and related Egger's regression suggested the possibility of a 'small-study effect' (larger effects in PCs when RRs are more imprecise) (Annex F, Figures F.1 and F.2). This can be interpreted as publication bias (e.g., study results not published or not located) or can be explained by actual heterogeneity (e.g., differences in the underlying risk across populations), outcome reporting or poor quality of small studies. The PC driving the asymmetry of the funnel plot was a cohort of Finnish males and females (FMCHES) with very low incidence of T2DM.

3.2.2. Fruit juices

3.2.2.1. Forest plots and pooled estimates

The relationship between the intake of FJs and incidence of T2DM was investigated in nine studies of which eight were PCs and one was a PCC. In the CARDIA cohort the endpoint was high fasting glucose (>110 mg/dL) or the use of hypoglycaemic medications.

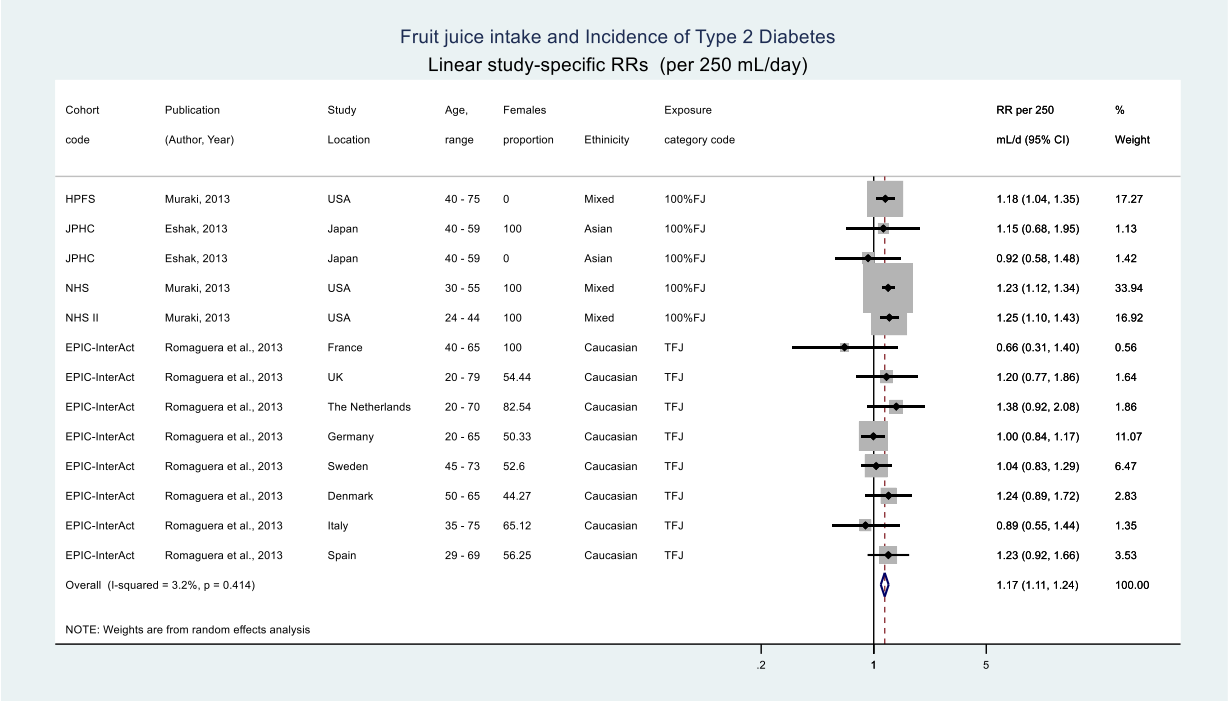


Individual-study effect estimates from most adjusted models are sorted by cohort and increasing exposure.

Figure 4: Forest plot – prospective associations of fruit juices intake with incidence of T2DM

3.2.2.2. Dose–response model

Forty-two non-referent RRs from 13 study-specific analyses (five PCs: 241,298 subjects and 24,706 cases) were included in the dose–response meta-analysis (I^2 = 3%; p = 0. 414). The BWHS (RRs not adjusted for BMI and EI), CARDIA (RR already provided per unit increase), SUN and WHI (model diagnostics) cohorts were excluded. Main characteristics of included studies are summarised in Table A.2 (Appendix A).

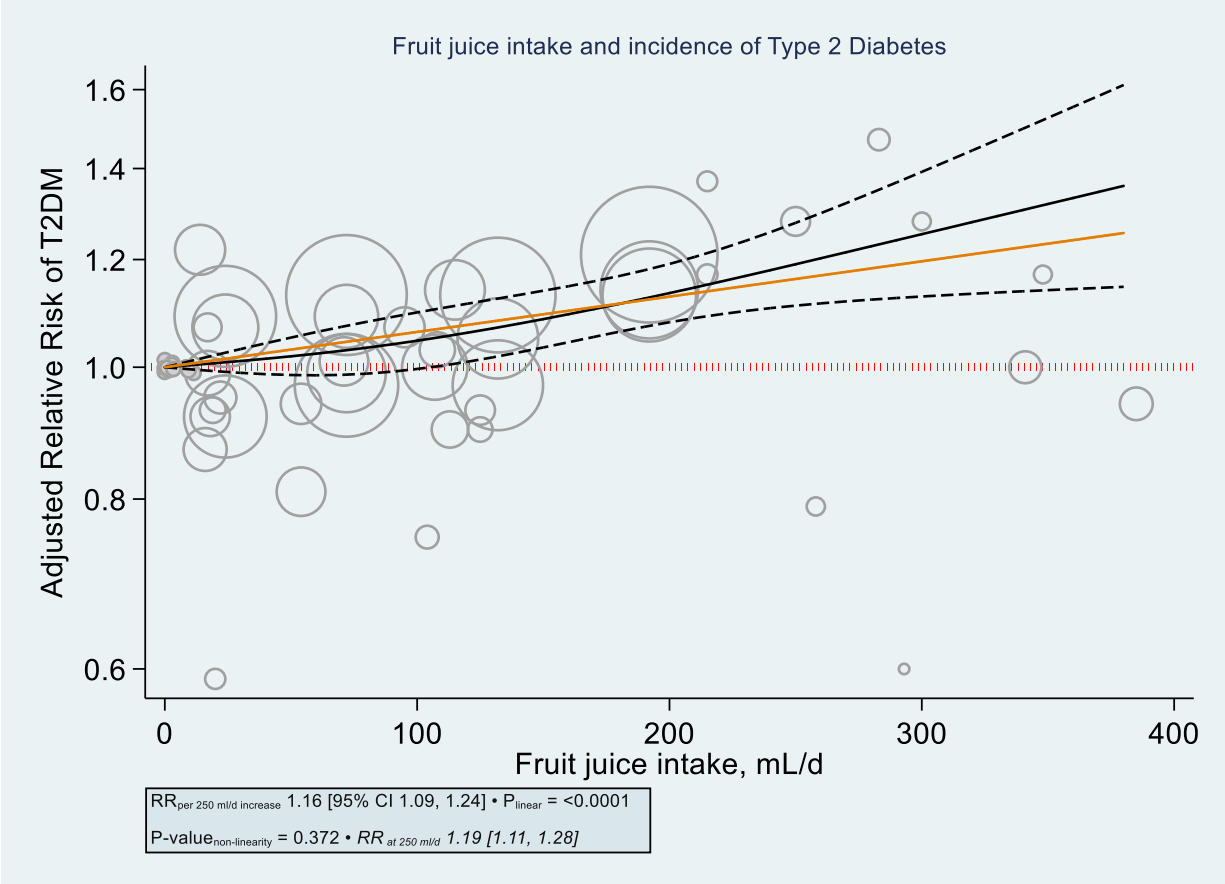


Individual-study RRs estimated per 250 mL/day increase in SSBs consumption are sorted by cohort; a pooled risk estimate is provided with its 95% confidence interval and between-study heterogeneity is quantified using the I^2 statistics and tested using the Cochrane Q statistics (p-value reported).

Figure 5: Forest plot – prospective associations of fruit juices intake with Incidence of T2DM included in the dose–response meta-analysis

Main results

The predicted pooled RR of T2DM for an increase in FJs intake of 250 ml/d was 1.16 (95% CI: 1.09, 1.24) assuming a linear dose–response relationship (p for linear trend < 0.0001), while it was 1.19 (95% CI: 1.11, 1.28) at 250 ml/d in the non-linear model (RCS with three knots at fixed percentiles, 10%, 50%, and 90%, of the distribution; p for non-linearity = 0.372) (Figure 6). Exposure scores were assigned mostly as mean/median and midrange values, with no points assigned with the most uncertain approach (Figure C.1, Appendix C). The decorrelated residuals-versus-exposure plot assessing the goodness-of-fit of the model is reported in Appendix B (Figure B.2). Predicted RRs (with their 95% CI) by relevant intakes from both the linear and the non-linear model are reported in Table G.2 (Appendix G).



Individual-study relative risk estimates from most adjusted models are plotted on the log scale and are represented by circles that are proportionate to their weight in the mixed model. The orange line represents the linear, and the black line represents the non-linear model, respectively, while the dotted red line is the reference (RR = 1). Dashed lines represent the 95% CI for the spline model. The value of 0 mL/day intake served as reference.

Figure 6: Linear and non-linear dose–response relationship between fruit juices intake and incidence of T2DM

Subgroup analyses, sensitivity analyses and publication bias

All subgroup results were interpreted only qualitatively, and summary estimates compared by visual inspection (I^2 range: 0–21%). The stratified analyses did not identify clear sources of heterogeneity, also given the overall heterogeneity quantified as 3% (Table 2).

Table 2: Subgroup analyses results on RR of T2DM per unit increase in FJs are summarised below and displayed in forest plots in Appendix D. I^2 is the estimated proportion of variance due to heterogeneity in each subgroup; the p-value of the test for heterogeneity based on Cochran's Q statistic is reported in the last column

	Subgroups	N studies	N subjects	RR	95% CI		I^2	p
All	**Adults**	13	241298	1.17	1.11	1.24	3%	0.414
Age	**Adults < 55 years**	5	192824	1.17	1.08	1.27	3%	0.389
	Adults ≥ 55 years	2	48474	1.14	1.03	1.26	0%	0.83
Sex	**Females**	3	166657	1.23	1.15	1.33	0%	0.941
	Males	2	48310	1.16	1.02	1.32	0%	0.322

	Mixed	8	26331	1.07	0.97	1.19	0%	0.502
Study location	**United States**	3	187382	1.22	1.15	1.30	0%	0.818
	Europe	8	26331	1.07	0.97	1.19	0%	0.502
	Asia	2	27585	1.02	0.72	1.45	0%	0.546
Follow-up time	**≤10 years**	2	27585	1.02	0.72	1.45	0%	0.546
	> 10 years	11	213713	1.17	1.10	1.25	12%	0.329
Tier	**Tier 1**	1	36173	1.18	1.04	1.35	-	-
	Tier 2	10	177540	1.16	1.07	1.25	21%	0.251
	Tier 3	2	27585	1.02	0.72	1.45	0%	0.546

A sensitivity analysis excluding RoB tier 3 studies confirmed no evidence of departure from linearity (p = 0.704) and showed similar RRs estimates [(1.17; 95% CI: 1.09, 1.25), (1.18; 95% CI: 1.10, 1.27)] and improved fitting (Figure E.3, Appendix E). A sensitivity analysis including a study that applied a different analytical approach (Standardised for Total Energy Intake; (Auerbach et al., 2017)) showed no evidence of departure from linearity (p = 0.315) and decreased RRs estimates [(1.12; 95% CI: 1.03, 1.20), (1.13; 95% CI: 1.04, 1.23)] (Figure E.4, Appendix E).

The funnel plot and related Egger's regression did not support a possible small-study effect (Annex F, Figures F.3 and F.4).

3.3. Risk of dyslipidaemia

The characteristics of the eligible observational studies for this endpoint are summarised in evidence tables in **Annex J** to the scientific opinion following the same order by exposure.

The outcome of the RoB assessment of the same studies is summarised in heatmap tables in **Appendix L** to the scientific opinion following the same order by exposure within the same endpoint.

Forest plots to visualise and interpret the effect estimates across studies have been produced for the following exposures: added (and free) sugars, SSBs, FJs. They are reported in **Appendix K** to the scientific opinion (**Figure K12**).

3.4. Risk of hypertension

The characteristics of the eligible observational studies for this endpoint are summarised in evidence tables in **Annex J** to the scientific opinion following the same order by exposure.

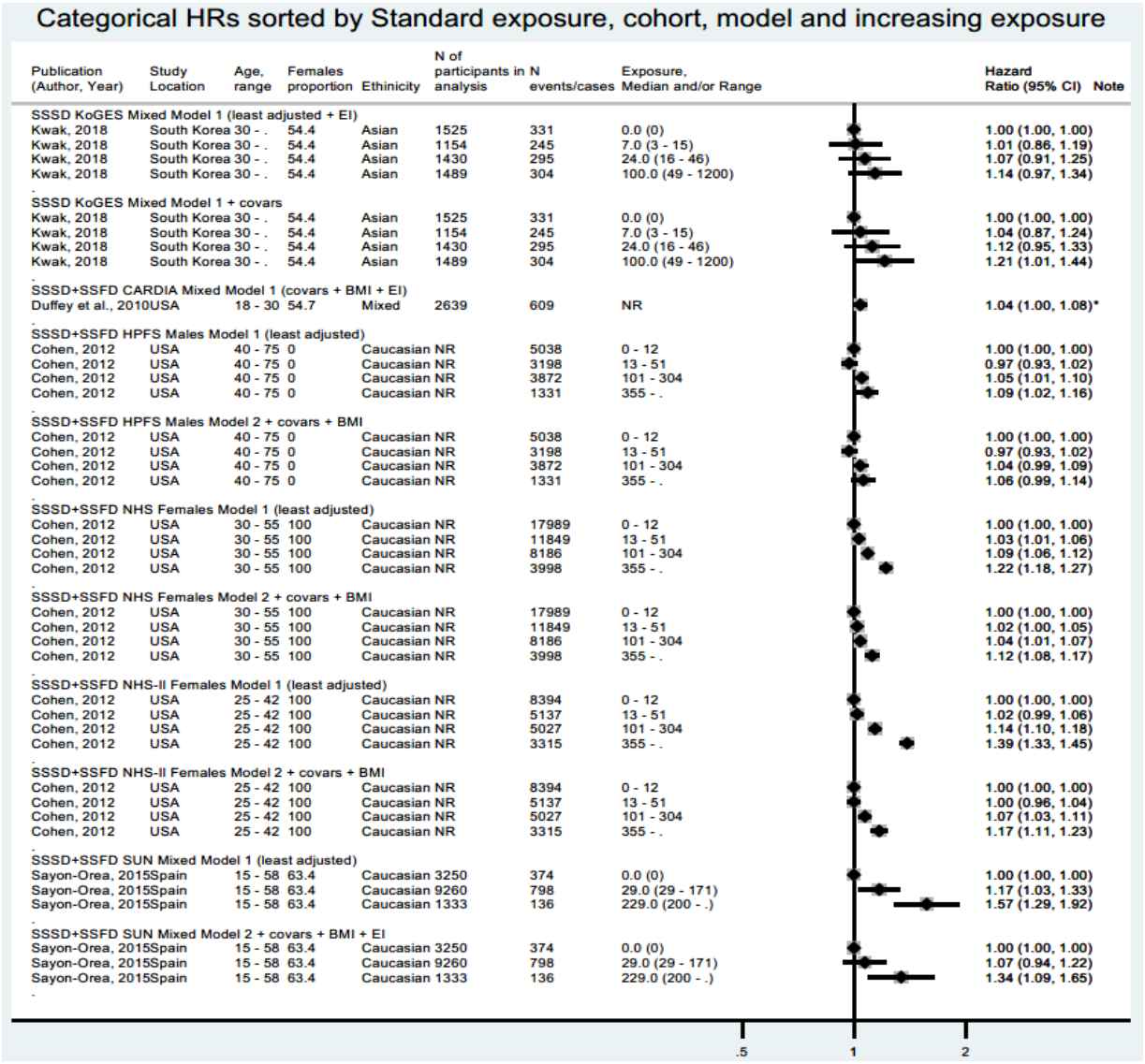
The outcome of the RoB assessment of the same studies is summarised in heatmap tables in **Appendix L** to the scientific opinion following the same order by exposure within the same endpoint.

Forest plots to visualise and interpret the effect estimates across studies were produced for the following exposures: fructose, SSBs. They are reported in **Appendix K** to the scientific opinion (**Figures K13 and K14**). A dose–response meta-analysis was carried out for the relationship between consumption of SSBs and risk of hypertension (HTN).

3.4.1. Sugar-sweetened beverages

3.4.1.1. Forest plots and pooled estimates

Seven PCs, six in adults and one in children and adolescents (TLGS), investigated the relationship between intake of SSBs and incidence of hypertension.

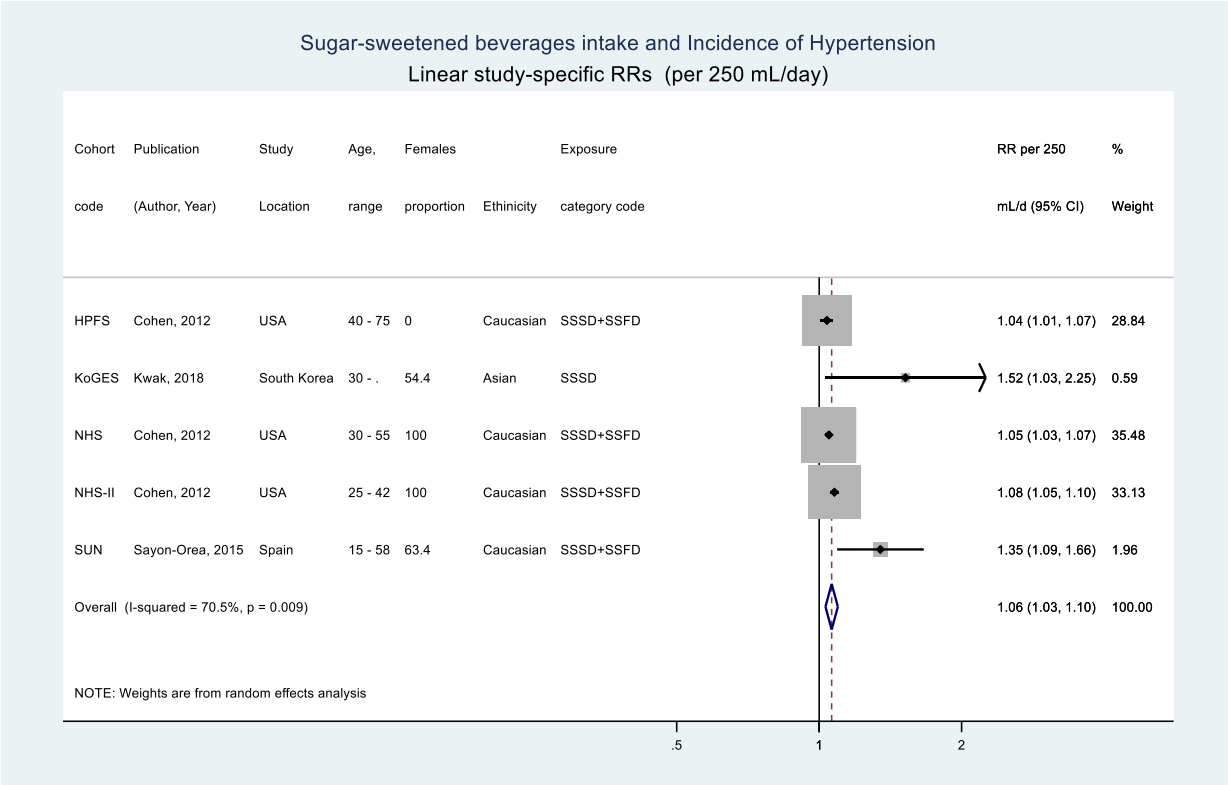


Individual-study effect estimates from all adjusted models are sorted by STD exposure, cohort, model and increasing exposure.

Figure 7: Forest plot – prospective associations of SSBs intake with incidence of hypertension

3.4.1.2. Dose–response model

Fourteen RRs from five study-specific analyses (243509 subjects and 79817 cases) were included in the dose–response meta-analysis (I^2 = 70.5%; p = 0.009). The TLGS (number of incident cases not reported) and CARDIA (RR already provided per unit increase) cohorts were excluded. Main characteristics of included studies are summarised in Table A.3 (Appendix A).

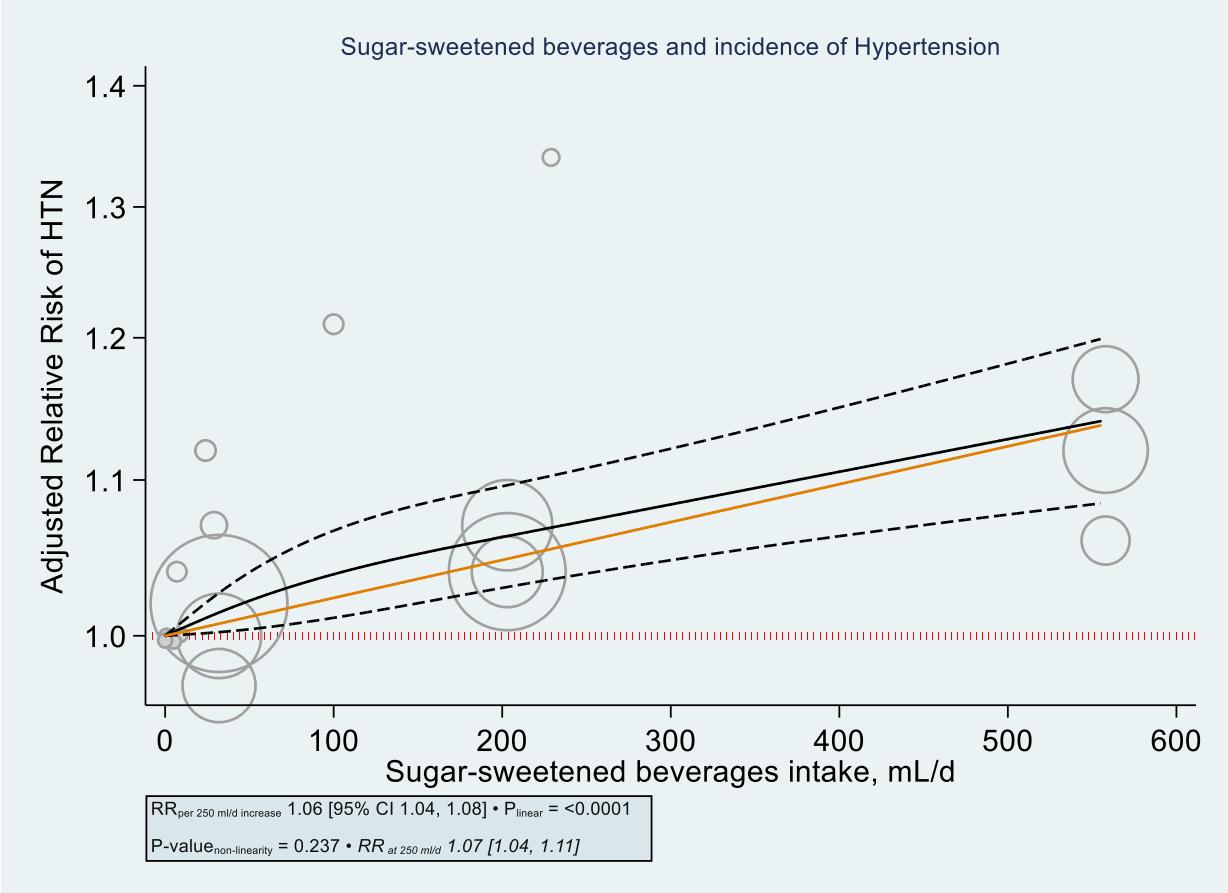


Individual-study RRs estimated per 250 mL/day increase in SSBs consumption are sorted by cohort; a pooled risk estimate is provided with its 95% confidence interval and between-study heterogeneity is quantified using the I^2 statistics and tested using the Cochrane Q statistics (p-value reported).

Figure 8: Forest plot – prospective associations of SSBs intake with incidence of HTN included in the dose–response meta-analysis

Main results

The predicted pooled RR of HTN for an increase in SSBs intake of 250 ml/d was 1.06 (95% CI: 1.04, 1.08) assuming a linear dose–response relationship (p for linear trend < 0.0001), while it was 1.07 (95% CI: 1.04, 1.11) at 250 ml/d in the non-linear model (RCS with three knots at fixed percentiles, 10%, 50%, and 90%, of the distribution; p for non-linearity = 0.237) (Figure 9). Exposure scores were assigned mostly as mean/median and midrange values, with points in the highest boundary of the exposure range assigned with a more uncertain approach (Figure C.1, Appendix C). The decorrelated residuals-versus-exposure plot assessing the goodness-of-fit of the model is reported in Appendix B (Figure B.3). Predicted RRs (with their 95% CI) by relevant intakes from both the linear and the non-linear model are reported in Table G.3 (Appendix G).



Individual-study relative risk estimates from most adjusted models are plotted on the log scale and are represented by circles that are proportionate to their weight in the mixed model. The orange line represents the linear, and the black line represents the non-linear model, respectively, while the dotted red line is the reference (RR = 1). Dashed lines represent the 95% CI for the spline model. The value of 0 mL/day intake served as reference.

Figure 9: Linear and non-linear dose–response relationship between sugars-sweetened beverages intake and incidence of hypertension

Subgroup analyses, sensitivity analyses and publication bias

All subgroup results were interpreted only qualitatively, and summary estimates compared by visual inspection (I^2 range: 0–77%). The stratified analyses did not identify clear sources of heterogeneity, also given the limited number of studies across strata (Table 3).

Table 3: Subgroup analyses results on RR of HTN per unit increase in SSBs are summarised below and displayed in forest plots in Appendix D. I^2 is the estimated proportion of variance due to heterogeneity in each subgroup; the p-value of the test for heterogeneity based on Cochran's Q statistic is reported in the last column

	Subgroups	N studies	N subjects	RR	95% CI		I^2	p
All	**Adults**	5	243509	1.06	1.03	1.10	71%	0.009
Age	**Adults < 55 years**	3	200374	1.07	1.03	1.11	77%	0.013
	Adults ≥ 55 years	2	43135	1.19	0.83	1.71	73%	0.056
Sex	**Females**	2	186531	1.06	1.04	1.09	73%	0.056
	Males	1	37360	1.04	1.01	1.07	-	-
	Mixed	2	19618	1.39	1.15	1.67	0%	0.59

Study location	**United States**	3	223891	1.06	1.04	1.08	61%	0.078
	Europe	1	13843	1.35	1.09	1.66	-	-
	Asia	1	5775	1.52	1.03	2.25	-	-
Follow-up time	**≤15 years**	2	19618	1.39	1.15	1.67	0%	0.59
	> 15 years	3	223891	1.06	1.04	1.08	61%	0.078
Tier	**Tier 1**	4	237734	1.06	1.03	1.09	71%	0.017
	Tier 2	1	5775	1.52	1.03	2.25	-	-

The funnel plot and related Egger's regression were not carried out as the number of studies was very limited.

3.5. Risk of cardiovascular diseases

The characteristics of the eligible observational studies for this endpoint are summarised in evidence tables in **Annex J** to the scientific opinion following the same order by exposure.

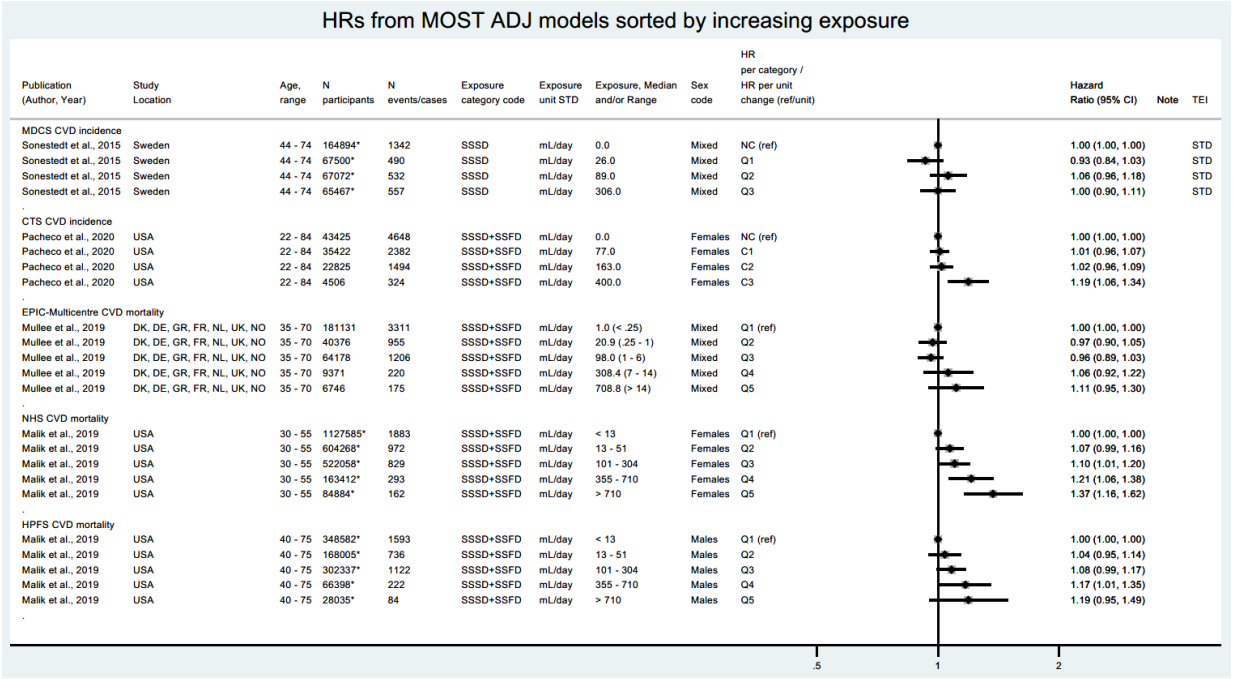
The outcome of the RoB assessment of the same studies is summarised in heatmap tables in **Appendix L** to the scientific opinion following the same order by exposure within the same endpoint.

Forest plots to visualise and interpret the effect estimates across studies were produced for the following exposures: total sugars, fructose, SSBs. They are reported in **Appendix K** of the scientific opinion (**Figures K15–K17**). A dose–response meta-analysis was carried out for the relationship between consumption of SSBs and risk of CVD.

3.5.1. Sugar-sweetened beverages

3.5.1.1. Forest plots and pooled estimates

Five PCs report on the relationship between SSBs consumption and CVD (composite endpoint) incidence (MDCS, CTS) or mortality (EPIC-Multicentre, NHS, HPFS), of which MDCS, CTS and EPIC-Multicentre also have coronary heart disease (CHD) and stroke as separate endpoints and NHS, HPFS also report on incidence of stroke in separate publications.

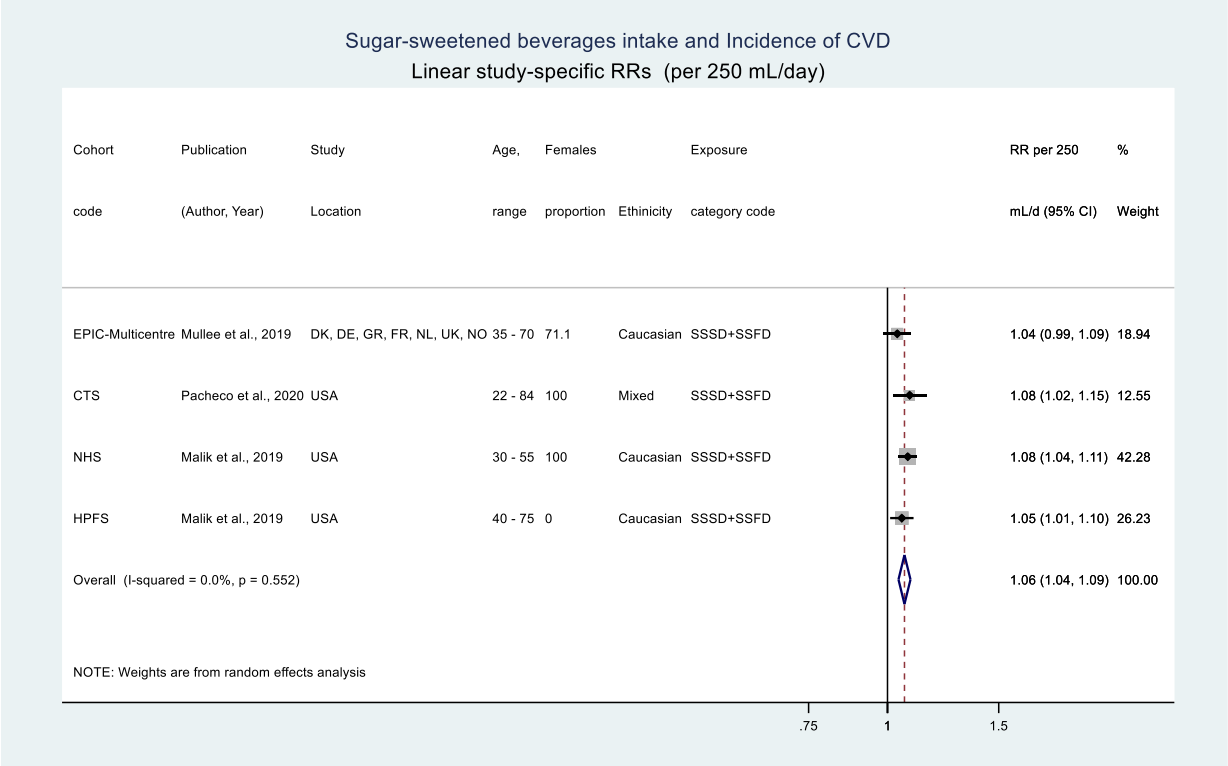


Individual-study effect estimates from most adjusted models are sorted by source, cohort and increasing exposure.

Figure 10: Forest plot – prospective associations of SSBs intake with incidence of CVD

3.5.1.2. Dose–response model

Fifteen RRs from four study-specific analyses (549521 subjects and 22611 cases) were included in the dose–response meta-analysis (I^2 = 0%; p = 552). The MDCS cohort was excluded (model diagnostics). Main characteristics of included studies are summarised in Table A.4 (Appendix A).

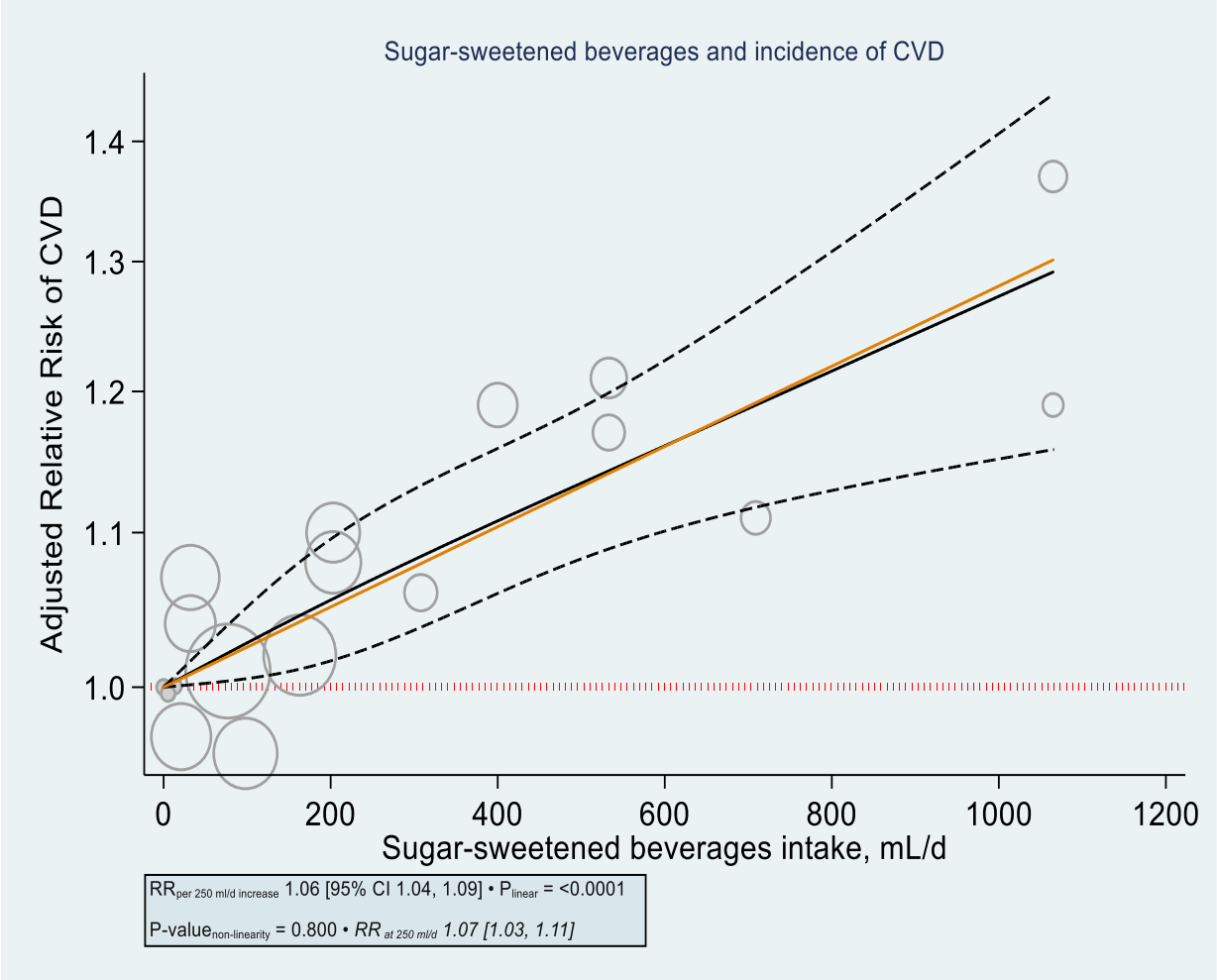


Individual-study RRs estimated per 250 mL/day increase in SSBs consumption are sorted by cohort; a pooled risk estimate is provided with its 95% confidence interval and between-study heterogeneity is quantified using the I^2 statistics and tested using the Cochrane Q statistics (p-value reported).

Figure 11: Forest plot – prospective associations of SSBs intake with incidence of CVD included in the dose–response meta-analysis

Main results

The predicted pooled RR of CVD (composite endpoint) for an increase in SSBs intake of 250 ml/d was 1.06 (95% CI: 1.04, 1.09) assuming a linear dose–response relationship (p for linear trend < 0.0001), while it was 1.07 (95% CI: 1.03, 1.11) at 250 ml/d in the non-linear model (RCS with three knots at fixed percentiles, 10%, 50%, and 90%, of the distribution; p for non-linearity = 0.800) (Figure 12). Exposure scores were assigned mostly as mean/median values, with points in the highest boundary of the exposure range assigned using a more uncertain approach (Figure C.1, Appendix C). The decorrelated residuals-versus-exposure plot assessing the goodness-of-fit of the model is reported in Appendix B (Figure B.4). Predicted RRs (with their 95% CI) by relevant intakes from both the linear and the non-linear model are reported in Table G.4 (Appendix G).



Individual-study relative risk estimates from most adjusted models are plotted on the log scale and are represented by circles that are proportionate to their weight in the mixed model. The orange line represents the linear, and the black line represents the non-linear model, respectively, while the dotted red line is the reference (RR = 1). Dashed lines represent the 95% CI for the spline model. The value of 0 mL/day intake served as reference.

Figure 12: Linear and non-linear dose–response relationship between sugars-sweetened beverages intake and incidence of cardiovascular diseases (composite endopoint)

Subgroup analyses, sensitivity analyses and publication bias

All subgroup results were interpreted only qualitatively, and summary estimates compared by visual inspection (I^2 range: 0–35%). The subgroup analyses did not identify clear sources of heterogeneity, also given the limited number of studies across strata (Table 4).

Table 4: Subgroup analyses results on RR of CVD per unit increase in SSBs are summarised below and displayed in forest plots in Appendix D. I^2 is the estimated proportion of variance due to heterogeneity in each subgroup; the p-value of the test for heterogeneity based on Cochran's Q statistic is reported in the last column

	Subgroups	N studies	N subjects	RR	95% CI		I^2	p
All	**Adults**	4	549521	1.06	1.04	1.09	0%	0.552
Age	**Adults < 53 years**	2	405627	1.06	1.02	1.10	35%	0.215
	Adults ≥ 53 years	2	143894	1.06	1.03	1.10	0%	0.453

Sex	**Females**	2	186825	1.08	1.05	1.11	0%	0.844
	Males	1	37716	1.05	1.01	1.10	-	-
	Mixed	1	324980	1.04	0.99	1.09	-	-
Study location	**United States**	3	224541	1.07	1.05	1.10	0%	0.667
	Europe	1	324980	1.04	0.99	1.09	-	-
Follow-up time	**≤20 years**	2	431158	1.06	1.01	1.10	20%	0.264
	> 20 years	2	118363	1.07	1.04	1.10	0%	0.435
Exposure referent category	**Referent other than NC**	3	443343	1.06	1.04	1.09	0%	0.431
	Non-consumers as referent	1	106178	1.08	1.02	1.15	-	-

A sensitivity analysis including a study that applied a different analytical approach (STD for Total Energy Intake; Sonestedt et al., 2015) showed no evidence of departure from linearity (p = 0.939) and decreased RRs estimates [(1.06; 95% CI: 1.04, 1.08), (1.06; 95% CI: 1.02, 1.10)] (Figure E.5, Appendix E).

The funnel plot and related Egger's regression were not carried out as the number of studies was very limited.

3.6. Risk of gout

The characteristics of the eligible observational studies for this endpoint are summarised in evidence tables in **Annex J** to the scientific opinion following the same order by exposure.

The outcome of the RoB assessment of the same studies is summarised in heatmap tables in **Appendix L** to the scientific opinion following the same order by exposure within the same endpoint.

Forest plots to visualise and interpret the effect estimates across studies have been produced for the following exposures: fructose, SSBs, FJs. They are reported in **Appendix K** to the scientific opinion (**Figures K18–K20**).

3.7. Analysis of uncertainties

Sources of uncertainty specific to the statistical analysis and their potential impact on the final estimates, when possible, were identified and described. Results from the sensitivity analyses further contributed to the interpretation of the dose–response results and together with the following additional considerations informed the overall assessment of the uncertainty in the body of evidence:

- It was not possible to explore all relevant and significant moderators in a quantitative way given the complexity of the analytical model and the relatively small number of studies per relationship.
- Sex-specific estimates were considered as independent contrasts; this may have caused a spurious increased precision.
- It has been shown that different choices in the exposure scores estimation may have impact on the dose–response results.
- The Greenland and Longnecker approach (Greenland and Longnecker, 1992), which takes into account the covariance of RRs sharing the same reference, has limitations, especially for dichotomous outcomes.
- General considerations around dose–response meta-analysis also apply: the model is a representation of the relationship between mean RRs of disease and mean intakes at 'group' level (aggregated data), it may be different when explored on individual data (aggregation bias) (Higgins and Thompson, 2004).

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Appendix A – Main characteristics of studies included in the dose–response meta-analysis

Table A.1 Studies included in the sugar-sweetened beverages and T2DM dose-response meta-analysis

Publication	Cohort	Country	Participants	Follow-up years	Age range in years	Sex	Population	Ethnicity	Standardised exposure	Tier of reliability
de Koning, 2011	HPFS	USA	40389	20	40–75	Males	Health professionals	Caucasian	SSSD+SSFD	1
Ericson, 2018	MDCS	Sweden	26622	18.4	45–73	Mixed	General population	Caucasian	SSSD+SSFD	3
Eshak, 2013	JPHC	Japan	15448	10	40–59	Females	General population	Asian	SSSD+SSFD+SSFJ	2
Eshak, 2013	JPHC	Japan	12137	10	40–59	Males	General population	Asian	SSSD+SSFD+SSFJ	2
Huang, 2017	WHI	USA	64850	8.4	50–79	Females	Post-menopausal	Mixed	SSSD+SSFD+TFJ	3
Kang, 2017	KoGES	South Korea	3592	5.7	40–69	Females	General population	Asian	SSSD	3
Kang, 2017	KoGES	South Korea	3068	5.7	40–69	Males	General population	Asian	SSSD	3
Ma, 2016a	Framingham Offspring	USA	1685	14	30–59	Mixed	General population	Caucasian	SSSD+SSFD	1
Montonen, 2007	FMCHES	Finland	2360	12	40–69	Mixed	General population	Caucasian	SSSD	2
Paynter, 2006	ARIC	USA	6790	9	45–64	Females	General population	Mixed	SSSD+SSFD+TFJ	1
Paynter, 2006	ARIC	USA	5414	9	45–64	Males	General population	Mixed	SSSD+SSFD+TFJ	1
Romaguera, 2013	EPIC-InterAct	The Netherlands	2067	16	20–70	Mixed	General population	Caucasian	SSSD+SSFD	2
Romaguera, 2013	EPIC-InterAct	Germany	3487	16	20–65	Mixed	General population	Caucasian	SSSD+SSFD	2

Romaguera, 2013	EPIC-InterAct	Denmark	3919	16	50–65	Mixed	General population	Caucasian	SSSD+SSFD	2
Romaguera, 2013	EPIC-InterAct	France	765	16	40–65	Mixed	General population	Caucasian	SSSD+SSFD	2
Romaguera, 2013	EPIC-InterAct	Sweden	3460	16	45–73	Mixed	General population	Caucasian	SSSD+SSFD	2
Romaguera, 2013	EPIC-InterAct	UK	2072	16	20–79	Mixed	General population	Caucasian	SSSD+SSFD	2
Sakurai, 2014	Toyama	Japan	2037	7	35–55	Males	Factory workers	Asian	SSSD+SSFD+SSFJ	1
Schulze, 2004	NHS II	USA	91249	8	24–44	Females	Health professionals	Caucasian	SSSD+SSFD	2

Publication	Sex	Exposure groups	N of cases	Person years	Exposure score (mL/d)	ADJ RR	95% CI	
de Koning, 2011	Males	C1 (ref)	586	167462	0	1	1	1
de Koning, 2011	Males	C2	629	165515	25	1.09	0.97	1.22
de Koning, 2011	Males	C3	685	189851	101	1.07	0.95	1.2
de Koning, 2011	Males	C4	780	187709	330	1.24	1.09	1.4
de Koning, 2011	Mixed	NC (ref)	1746	221229	0	1	1	1
Ericson, 2018	Mixed	Q1	749	95790	24	1.02	0.94	1.12
Ericson, 2018	Mixed	Q2	723	85689	95	1.05	0.96	1.15
Ericson, 2018	Mixed	Q3	828	86478	238	1.05	0.96	1.14
Eshak, 2013	Females	C1 (ref)	200	98709	0	1	1	1
Eshak, 2013	Females	C2	83	35535	54	1.15	0.88	1.51
Eshak, 2013	Females	C3	30	12832	125	1.17	0.78	1.76
Eshak, 2013	Females	C4	27	7403	215	1.79	1.11	2.89
Eshak, 2013	Males	C1 (ref)	261	62604	0	1	1	1
Eshak, 2013	Males	C2	121	33820	54	0.86	0.68	1.08
Eshak, 2013	Males	C3	58	14152	125	0.98	0.68	1.42
Eshak, 2013	Males	C4	44	10794	215	0.98	0.68	1.42
Huang, 2017	Females	C1 (ref)	2751	334355	19	1	1	1

Huang, 2017	Females	C2	1108	128224	178	1.05	0.98	1.12
Huang, 2017	Females	C3	485	54085	355	1.09	0.97	1.23
Huang, 2017	Females	C4	331	28076	852	1.43	1.17	1.75
Kang, 2017	Females	NC (ref)	458	10170	0	1	1	1
Kang, 2017	Females	Q1	317	7817	16	0.9	0.78	1.04
Kang, 2017	Females	Q2	120	2176	71	1.23	1	1.51
Kang, 2017	Females	Q3	16	311	198	1.13	0.68	1.86
Kang, 2017	Males	NC (ref)	416	5622	0	1	1	1
Kang, 2017	Males	Q1	443	7487	16	0.8	0.7	0.92
Kang, 2017	Males	Q2	264	3676	71	0.97	0.82	1.13
Kang, 2017	Males	Q3	58	703	198	1.12	0.85	1.49
Ma, 2016a	Mixed	Q1 (ref)	191	5542	0	1	1	1
Ma, 2016a	Mixed	Q2	221	6471	26	0.99	0.81	1.2
Ma, 2016a	Mixed	Q3	207	6325	103	0.95	0.77	1.17
Ma, 2016a	Mixed	Q4	270	5252	309	1.49	1.2	1.86
Montonen, 2007	Mixed	Q1 (ref)	25	8233	0	1	1	1
Montonen, 2007	Mixed	Q2	12	4610	1	0.85	0.42	1.73
Montonen, 2007	Mixed	Q3	21	8562	13	0.8	0.43	1.49
Montonen, 2007	Mixed	Q4	33	6915	143	1.6	0.93	2.76
Paynter, 2006	Females	C1 (ref)	320	27438	108	1	1	1
Paynter, 2006	Females	C2	103	6815	240	1.13	0.91	1.42
Paynter, 2006	Females	C3	182	11255	360	1.1	0.91	1.33
Paynter, 2006	Females	C4	114	6533	672	1	0.79	1.29
Paynter, 2006	Males	C1 (ref)	331	19205	108	1	1	1
Paynter, 2006	Males	C2	67	3706	240	1.03	0.79	1.34
Paynter, 2006	Males	C3	182	10665	360	0.95	0.79	1.15
Paynter, 2006	Males	C4	138	6892	672	1.03	0.82	1.28
Romaguera, 2013	Mixed	C1 (ref)	229	4902.46	0	1	1	1
Romaguera, 2013	Mixed	C2	11	172.21	20	2.3	0.96	5.5
Romaguera, 2013	Mixed	C3	7	166.76	75	1.45	0.55	3.83
Romaguera, 2013	Mixed	C4	2	18.66	340	1.35	0.09	19.34

Romaguera, 2013	Mixed	C1 (ref)	359	6259.01	0	1	1	1
Romaguera, 2013	Mixed	C2	178	2768.04	18	1.36	0.98	1.88
Romaguera, 2013	Mixed	C3	233	3384.57	108	1.28	0.95	1.72
Romaguera, 2013	Mixed	C4	136	1356.18	308	1.58	1.01	2.46
Romaguera, 2013	Mixed	C1 (ref)	201	4314.98	0	1	1	1
Romaguera, 2013	Mixed	C2	144	4007.36	24	0.55	0.37	0.84
Romaguera, 2013	Mixed	C3	349	6678.25	90	0.95	0.64	1.42
Romaguera, 2013	Mixed	C4	48	1152.5	320	0.54	0.26	1.12
Romaguera, 2013	Mixed	C1 (ref)	1032	15801.21	0	1	1	1
Romaguera, 2013	Mixed	C2	193	2255.65	19	1.36	1.02	1.79
Romaguera, 2013	Mixed	C3	190	2744.33	85	1.01	0.77	1.31
Romaguera, 2013	Mixed	C4	118	862.28	407	1.73	1.15	2.6
Romaguera, 2013	Mixed	C1 (ref)	837	12589.95	0	1	1	1
Romaguera, 2013	Mixed	C2	120	1654	29	1.81	1.32	2.48
Romaguera, 2013	Mixed	C3	554	7868.87	94	1.15	0.94	1.39
Romaguera, 2013	Mixed	C4	190	1977.12	371	1.12	0.83	1.52
Romaguera, 2013	Mixed	C1 (ref)	1290	14803.93	0	1	1	1
Romaguera, 2013	Mixed	C2	318	3839.64	16	1.01	0.83	1.24
Romaguera, 2013	Mixed	C3	266	3199.11	86	0.91	0.73	1.14
Romaguera, 2013	Mixed	C4	111	1091.72	500	1.25	0.9	1.74
Sakurai, 2014	Males	C1 (ref)	55	3554	0	1	1	1
Sakurai, 2014	Males	C2	19	1494	28	0.97	0.57	1.64
Sakurai, 2014	Males	C3	72	4825	114	1.11	0.74	1.66
Sakurai, 2014	Males	C4	24	1381	498	1.34	0.72	2.36
Schulze, 2004	Females	C1 (ref)	368	381275	6	1	1	1
Schulze, 2004	Females	C4	115	66438	558	1.32	1.01	1.73

Table A.2 Studies included in the fruit juices and T2DM dose–response meta-analysis

Publication	Cohort	Country	Participants	Follow-up years	Age range in years	Sex	Population	Ethnicity	Standarised exposure	Tier of reliability
Eshak, 2013	JPHC	Japan	15448	10	40–59	Females	General population	Asian	100%FJ	3
Eshak, 2013	JPHC	Japan	12137	10	40–59	Males	General population	Asian	100%FJ	3
Muraki, 2013	HPFS	USA	36173	20	40–75	Males	Health professionals	Mixed	100%FJ	1
Muraki, 2013	NHS	USA	66105	24	30–55	Females	Health professionals	Mixed	100%FJ	2
Muraki, 2013	NHS II	USA	85104	18	24–44	Females	Health professionals	Mixed	100%FJ	2
Romaguera, 2013	EPIC-InterAct	France	765	16	40–65	Mixed	General population	Caucasian	TFJ	2
Romaguera, 2013	EPIC-InterAct	UK	2072	16	20–79	Mixed	General population	Caucasian	TFJ	2
Romaguera, 2013	EPIC-InterAct	The Netherlands	2067	16	20–70	Mixed	General population	Caucasian	TFJ	2
Romaguera, 2013	EPIC-InterAct	Germany	3487	16	20–65	Mixed	General population	Caucasian	TFJ	2
Romaguera, 2013	EPIC-InterAct	Sweden	5194	16	45–73	Mixed	General population	Caucasian	TFJ	2
Romaguera, 2013	EPIC-InterAct	Denmark	3919	16	50–65	Mixed	General population	Caucasian	TFJ	2
Romaguera, 2013	EPIC-InterAct	Italy	3188	16	35–75	Mixed	General population	Caucasian	TFJ	2
Romaguera, 2013	EPIC-InterAct	Spain	5639	16	29–69	Mixed	General population	Caucasian	TFJ	2

Publication	Sex	Exposure groups	N of cases	Person years	Exposure score (mL/d)	ADJ RR	95% CI

Eshak, 2013	Females	C1 (ref)	198	88916	0	1	1	1
Eshak, 2013	Females	C2	99	47152	54	0.94	0.73	1.24
Eshak, 2013	Females	C3	25	12574	125	0.9	0.58	1.4
Eshak, 2013	Females	C4	18	5838	215	1.37	0.79	2.37
Eshak, 2013	Males	C1 (ref)	302	71172	0	1	1	1
Eshak, 2013	Males	C2	129	37472	54	0.81	0.65	1.01
Eshak, 2013	Males	C3	36	9191	125	0.93	0.65	1.35
Eshak, 2013	Males	C4	17	3535	215	1.17	0.69	2
Muraki, 2013	Males	C1 (ref)	401	93948	12	1	1	1
Muraki, 2013	Males	C2	225	49856	24	1.07	0.91	1.26
Muraki, 2013	Males	C3	488	119407	72	0.99	0.86	1.13
Muraki, 2013	Males	C4	460	112021	132	1.05	0.92	1.2
Muraki, 2013	Males	C5	1113	279172	192	1.13	1.01	1.27
Muraki, 2013	Females	C1 (ref)	921	210618	12	1	1	1
Muraki, 2013	Females	C2	547	114927	24	1.09	0.98	1.21
Muraki, 2013	Females	C3	1260	263597	72	1.13	1.03	1.23
Muraki, 2013	Females	C4	1090	240853	132	1.13	1.03	1.24
Muraki, 2013	Females	C5	2540	564132	192	1.21	1.12	1.31
Muraki, 2013	Females	C1 (ref)	672	248276	12	1	1	1
Muraki, 2013	Females	C2	357	150182	24	0.92	0.81	1.05
Muraki, 2013	Females	C3	777	338127	72	0.97	0.87	1.07
Muraki, 2013	Females	C4	494	254371	132	0.97	0.86	1.09
Muraki, 2013	Females	C5	853	425155	192	1.14	1.02	1.27
Romaguera, 2013	Mixed	C1 (ref)	113	1997.08	0	1	1	1
Romaguera, 2013	Mixed	C2	32	1063.66	20	0.59	0.34	1
Romaguera, 2013	Mixed	C3	93	1958.11	104	0.75	0.47	1.21
Romaguera, 2013	Mixed	C4	11	241.22	293	0.6	0.21	1.75
Romaguera, 2013	Mixed	C1 (ref)	445	5808.06	0	1	1	1
Romaguera, 2013	Mixed	C2	98	1698.48	17	1.07	0.73	1.58
Romaguera, 2013	Mixed	C3	337	5849.58	95	1.07	0.82	1.4
Romaguera, 2013	Mixed	C4	26	411.69	300	1.28	0.7	2.35

Romaguera, 2013	Mixed	C1 (ref)	214	3726.43	0	1	1	1
Romaguera, 2013	Mixed	C2	90	2235.45	19	0.93	0.61	1.41
Romaguera, 2013	Mixed	C3	370	8993.09	108	1.03	0.76	1.4
Romaguera, 2013	Mixed	C4	68	1198.12	283	1.47	0.89	2.44
Romaguera, 2013	Mixed	C1 (ref)	197	2195.64	0	1	1	1
Romaguera, 2013	Mixed	C2	216	3238.83	22	0.95	0.68	1.33
Romaguera, 2013	Mixed	C3	740	11304.77	113	0.9	0.67	1.21
Romaguera, 2013	Mixed	C4	380	4924.23	385	0.94	0.68	1.31
Romaguera, 2013	Mixed	C1 (ref)	1195	14928.16	0	1	1	1
Romaguera, 2013	Mixed	C2	505	8190.32	16	0.87	0.68	1.12
Romaguera, 2013	Mixed	C3	687	11356.45	107	1	0.85	1.18
Romaguera, 2013	Mixed	C4	118	1933.5	341	1	0.71	1.39
Romaguera, 2013	Mixed	C1 (ref)	1070	12216.51	0	1	1	1
Romaguera, 2013	Mixed	C2	298	3274.54	14	1.22	0.99	1.52
Romaguera, 2013	Mixed	C3	552	6715.08	72	1.09	0.92	1.29
Romaguera, 2013	Mixed	C4	65	728.26	250	1.28	0.88	1.86
Romaguera, 2013	Mixed	C1 (ref)	696	11496.26	0	1	1	1
Romaguera, 2013	Mixed	C2	283	5270.37	18	0.92	0.7	1.21
Romaguera, 2013	Mixed	C3	311	5807.05	71	1.01	0.81	1.26
Romaguera, 2013	Mixed	C4	29	572.04	258	0.79	0.44	1.45
Romaguera, 2013	Mixed	C1 (ref)	1907	34272.16	0	1	1	1
Romaguera, 2013	Mixed	C2	180	3239.43	17	0.99	0.78	1.26
Romaguera, 2013	Mixed	C3	335	6419.46	115	1.14	0.95	1.36
Romaguera, 2013	Mixed	C4	23	416.54	348	1.17	0.64	2.15

Table A.3 Studies included in the sugar-sweetened beverages and hypertension dose–response meta-analysis

Publication	Cohort	Country	Participants	Follow-up years	Age range in years	Sex	Population	Ethnicity	Standarised exposure	Tier of reliability
Cohen et al. (2012)	NHS II	USA	97991	16	25–42	Females	Health professionals	Caucasian	SSSD+SSFD	1
Cohen et al. (2012)	NHS	USA	88540	28	30–55	Females	Health professionals	Caucasian	SSSD+SSFD	1
Cohen et al. (2012)	HPFS	USA	37360	22	40–75	Males	Health professionals	Caucasian	SSSD+SSFD	1
Kwak et al. (2018)	KoGES	South Korea	5775	8	>30	Mixed	General population	Asian	SSSD	2
Sayon-Orea et al. (2015)	SUN	Spain	13843	8.1	15–58	Mixed	Health professionals	Caucasian	SSSD+SSFD	1

Publication	Sex	Exposure groups	N of cases	Person years	Exposure score (mL/d)	ADJ RR	95% CI	
Cohen et al. (2012)	Females	C1 (ref)	17989	556939	6	1	1	1
Cohen et al. (2012)	Females	C2	11849	402891	32	1.02	0.99	1.04
Cohen et al. (2012)	Females	C3	8186	276384	203	1.04	1.01	1.07
Cohen et al. (2012)	Females	C4	3998	129827	558	1.12	1.08	1.17
Cohen et al. (2012)	Females	C1 (ref)	8394	456363	6	1	1	1
Cohen et al. (2012)	Females	C2	5137	307057	32	1	0.96	1.04
Cohen et al. (2012)	Females	C3	5027	303437	203	1.07	1.03	1.11
Cohen et al. (2012)	Females	C4	3315	176141	558	1.17	1.11	1.23
Cohen et al. (2012)	Males	C1 (ref)	5038	172999	6	1	1	1
Cohen et al. (2012)	Males	C2	3198	118553	32	0.97	0.93	1.02
Cohen et al. (2012)	Males	C3	3872	142434	203	1.04	1	1.1
Cohen et al. (2012)	Males	C4	1331	49658	558	1.06	0.99	1.14
Kwak et al. (2018)	Mixed	Q1 (ref)	331	7468	0	1	1	1
Kwak et al. (2018)	Mixed	Q2	245	5818	7	1.04	0.87	1.24
Kwak et al. (2018)	Mixed	Q3	295	6985	24	1.12	0.95	1.33

Kwak et al. (2018)	Mixed	Q4	304	7157	100	1.21	1.02	1.45
Sayon-Orea et al. (2015)	Mixed	C1 (ref)	374	23163	0	1	1	1
Sayon-Orea et al. (2015)	Mixed	C2	798	71542	29	1.07	0.94	1.22
Sayon-Orea et al. (2015)	Mixed	C3	136	10140	229	1.34	1.09	1.65

Table A.4 Studies included in the sugar-sweetened beverages and CVD dose–response meta-analysis

Publication	Cohort	Country	Participants	Follow-up years	Age range in years	Sex	Population	Ethnicity	Standarised exposure	Tier of reliability
Malik et al. (2019)	NHS	USA	80647	34	30–55	Females	Nurses	Caucasian	SSSD+SSFD	1
Malik et al. (2019)	HPFS	USA	37716	28	40–75	Males	Health professionals	Caucasian	SSSD+SSFD	1
Mullee et al. (2019)	EPIC-Multicentre	DK, DE, GR, FR, NL, UK, NO	324980	16.4	35–70	Mixed	General population	Caucasian	SSSD+SSFD	3
Pacheco et al. (2020)	CTS	USA	106178	20	22–84	Females	Teachers	Mixed	SSSD+SSFD	2

Publication	Sex	Exposure groups	N of cases	Person years	Exposure score (mL/d)	ADJ RR	95% CI	
Malik et al. (2019)	Females	Q1 (ref)	1883	1127585	7	1	1	1
Malik et al. (2019)	Females	Q2	972	604268	32	1.07	0.99	1.16
Malik et al. (2019)	Females	Q3	829	522058	203	1.1	1.01	1.2
Malik et al. (2019)	Females	Q4	293	163412	533	1.21	1.06	1.37
Malik et al. (2019)	Females	Q5	162	84884	1065	1.37	1.16	1.62
Malik et al. (2019)	Males	Q1 (ref)	1593	348582	7	1	1	1
Malik et al. (2019)	Males	Q2	736	168005	32	1.04	0.95	1.14
Malik et al. (2019)	Males	Q3	1122	302337	203	1.08	1	1.18
Malik et al. (2019)	Males	Q4	222	66398	533	1.17	1.01	1.35
Malik et al. (2019)	Males	Q5	84	28035	1065	1.19	0.95	1.49
Mullee et al. (2019)	Mixed	C1 (ref)	3311	2981842	1	1	1	1
Mullee et al. (2019)	Mixed	C2	955	887078	21	0.97	0.9	1.05
Mullee et al. (2019)	Mixed	C3	1206	1131137	98	0.96	0.9	1.04
Mullee et al. (2019)	Mixed	C4	220	187322	308	1.06	0.92	1.22
Mullee et al. (2019)	Mixed	Q5	175	142293	709	1.11	0.95	1.3
Pacheco et al. (2020)	Females	NC (ref)	4648	1128938	0	1	1	1
Pacheco et al. (2020)	Females	C1	2382	572727	77	1.01	0.96	1.07

Pacheco et al. (2020)	Females	C2	1494	355829	163	1.02	0.96	1.09
Pacheco et al. (2020)	Females	C3	324	66065	400	1.19	1.06	1.34

Appendix B – Dose–response model fitting

In the decorrelated residuals-versus-exposure plots the black points are the decorrelated residuals and the solid red line is an overlayed locally weighted scatterplot smoother (LOWESS). The vertical distances from the reference line (0) are not directly interpretable, however, the pooled dose–response curve fits perfectly the data according to the exposure levels whenever all the points lie on the reference line (horizontal dotted line).

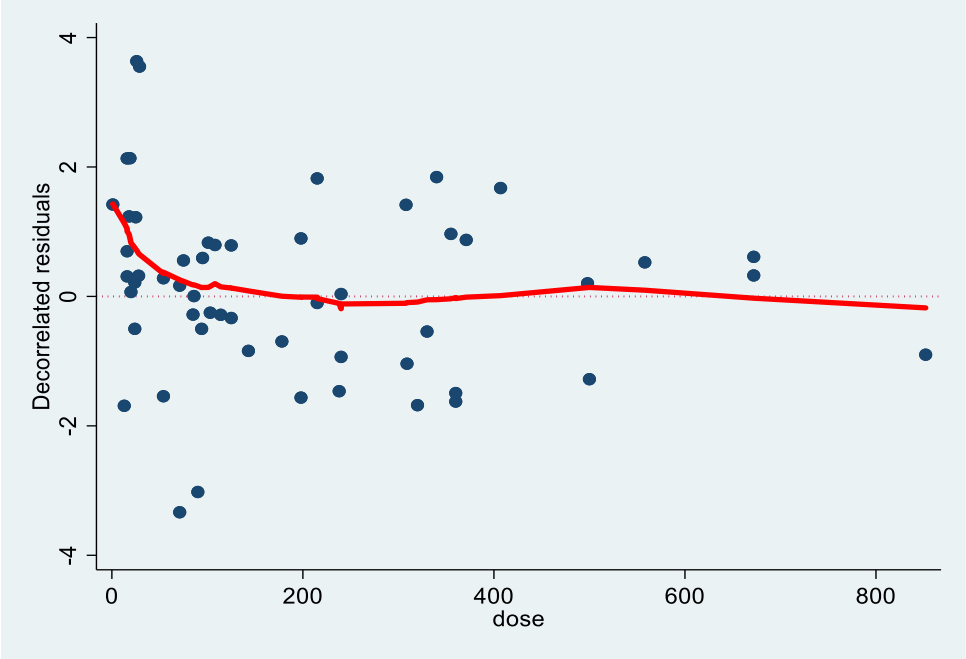


Figure B.1 SSBs and T2DM – decorrelated residuals from final dose–response model

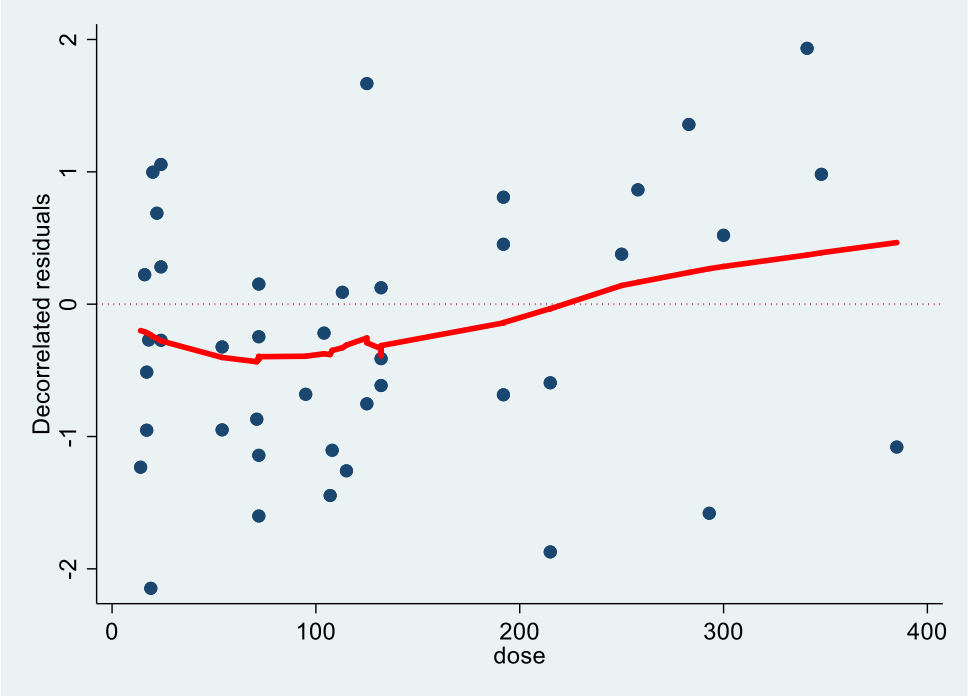


Figure B.2 FJs and T2DM – decorrelated residuals from final dose–response model

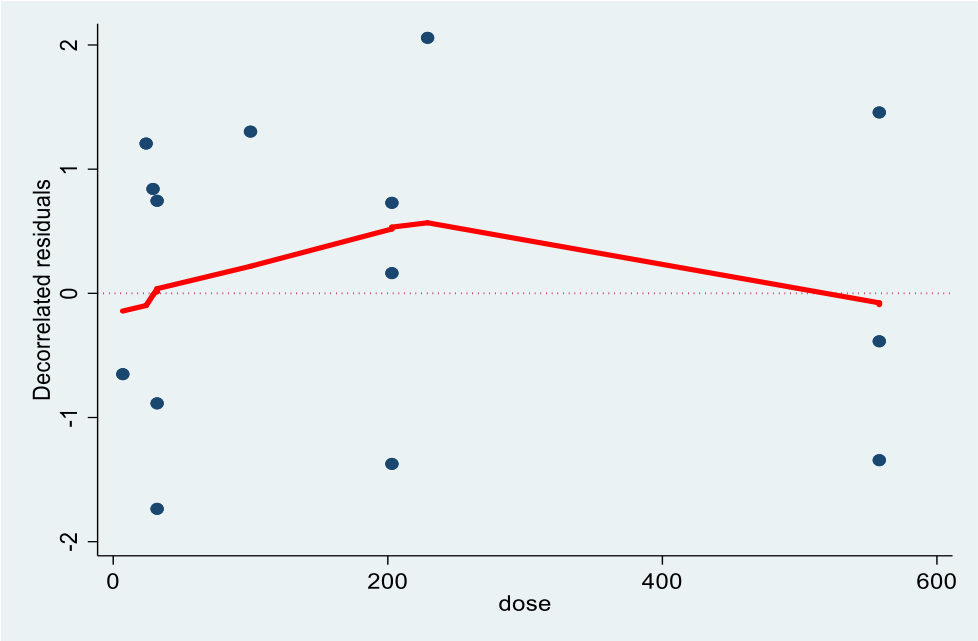


Figure B.3 SSBs and HTN – decorrelated residuals from final dose–response model

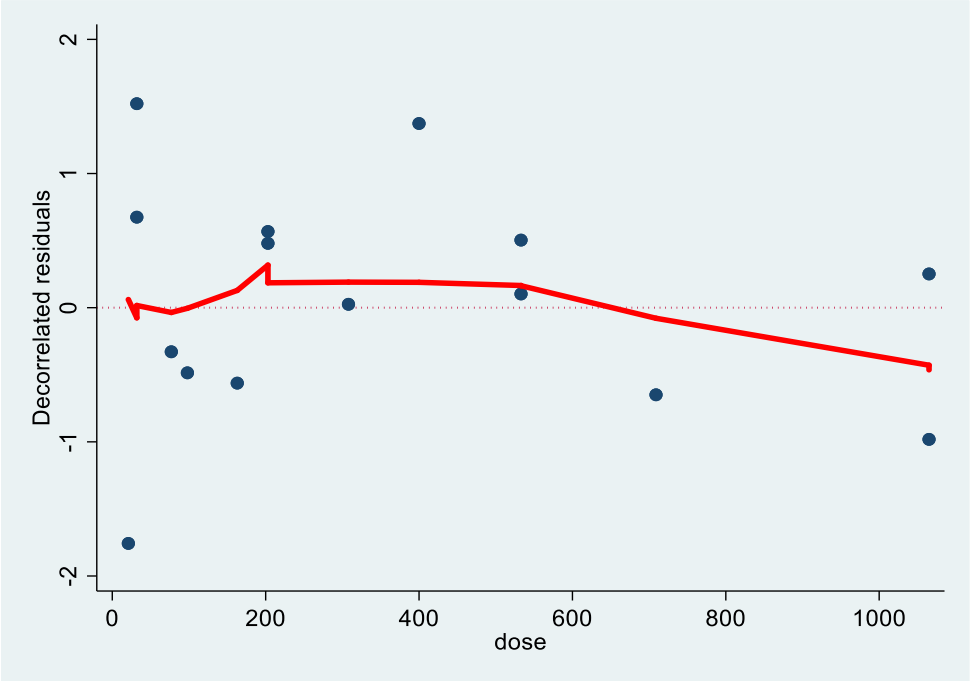


Figure B.4 SSBs and CVD – decorrelated residuals from final dose–response model

Appendix C – Exposure scores assignment

Each scatterplot illustrates the assignments according to data availability and related approaches (numbers identifies categories from same individual studies): blue scores are assigned as mean/median available values; red scores are assigned as midpoint of the reported range (mean/median not available); green scores are assigned as lower boundary value + the width of the second-highest category (Il'yasova et al. (2005), to upper open-ended categories); orange scores are assigned as lower boundary value * 1.2 (Berlin et al. (1993), when the second-highest category has width equal to 0). Uncertainty in score assignment increases while moving from approach 1 (blue) to approach 4 (orange).

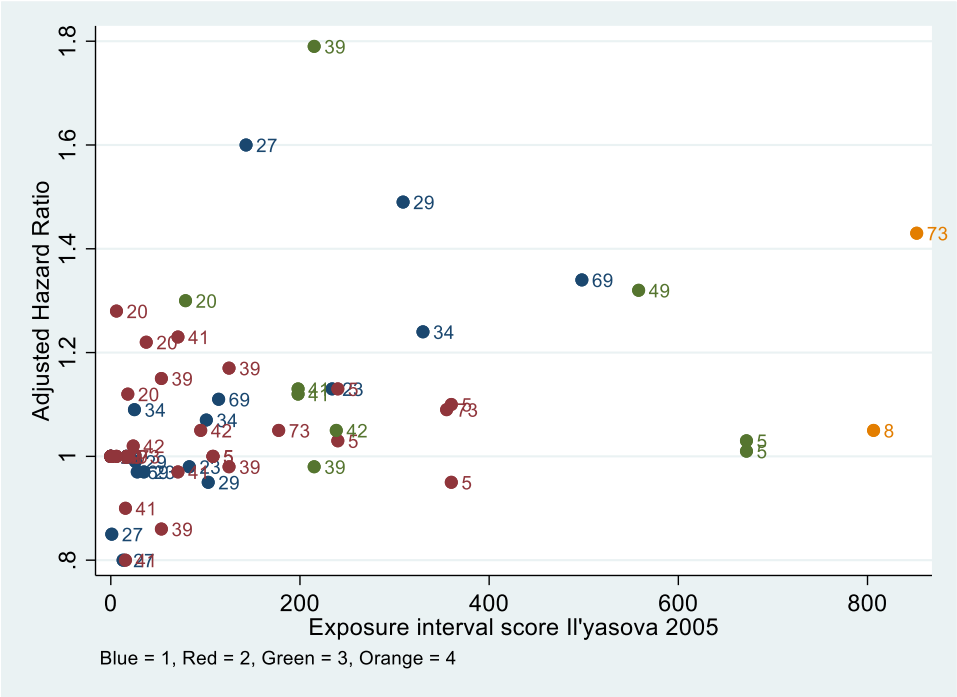


Figure C.1 Exposure scores from the SSBs and T2DM dose–response meta-analysis

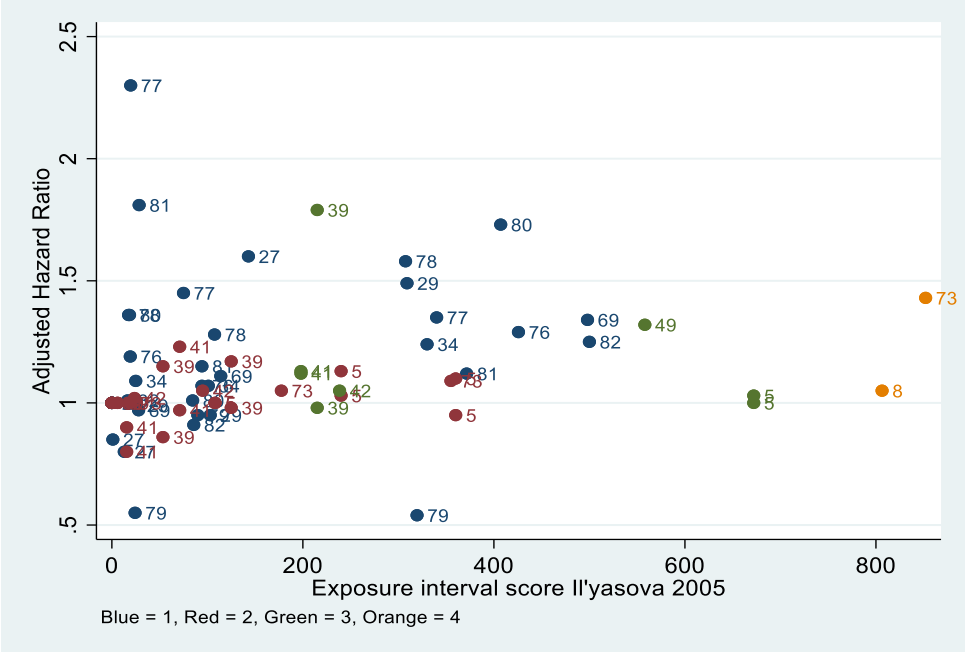


Figure C.2 Exposure scores from the FJs and T2DM dose–response meta-analysis

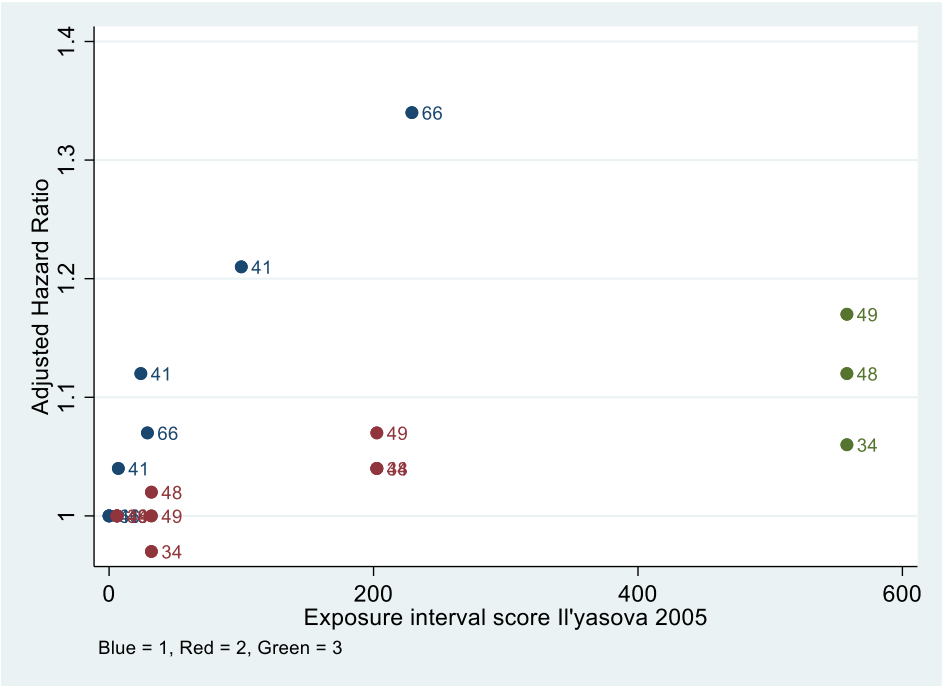


Figure C.3 Exposure scores from the SSBs and HTN dose–response meta-analysis

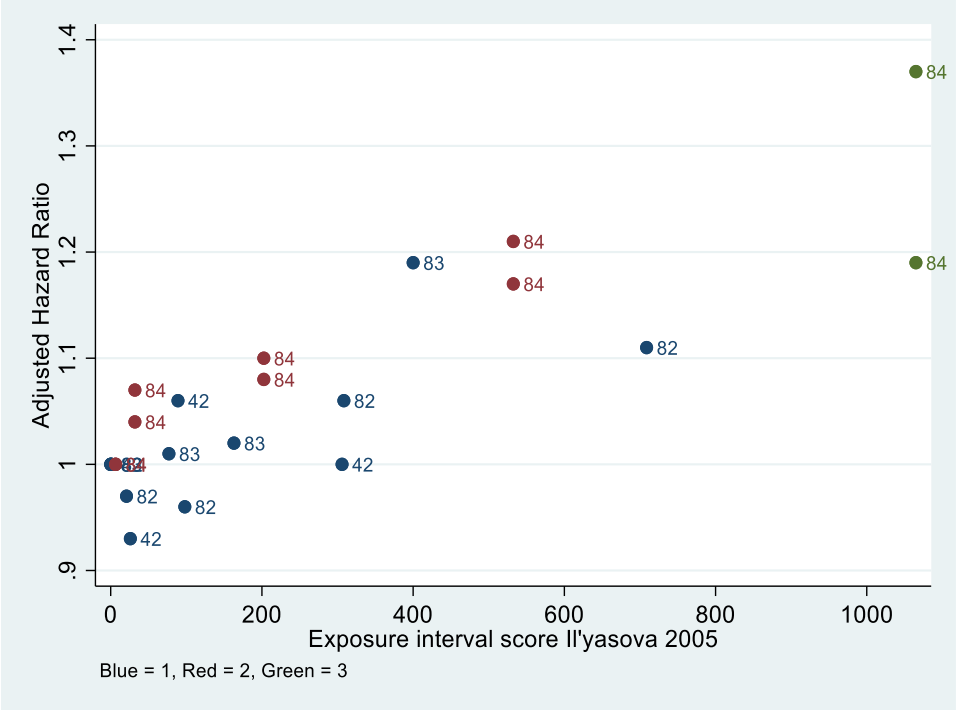
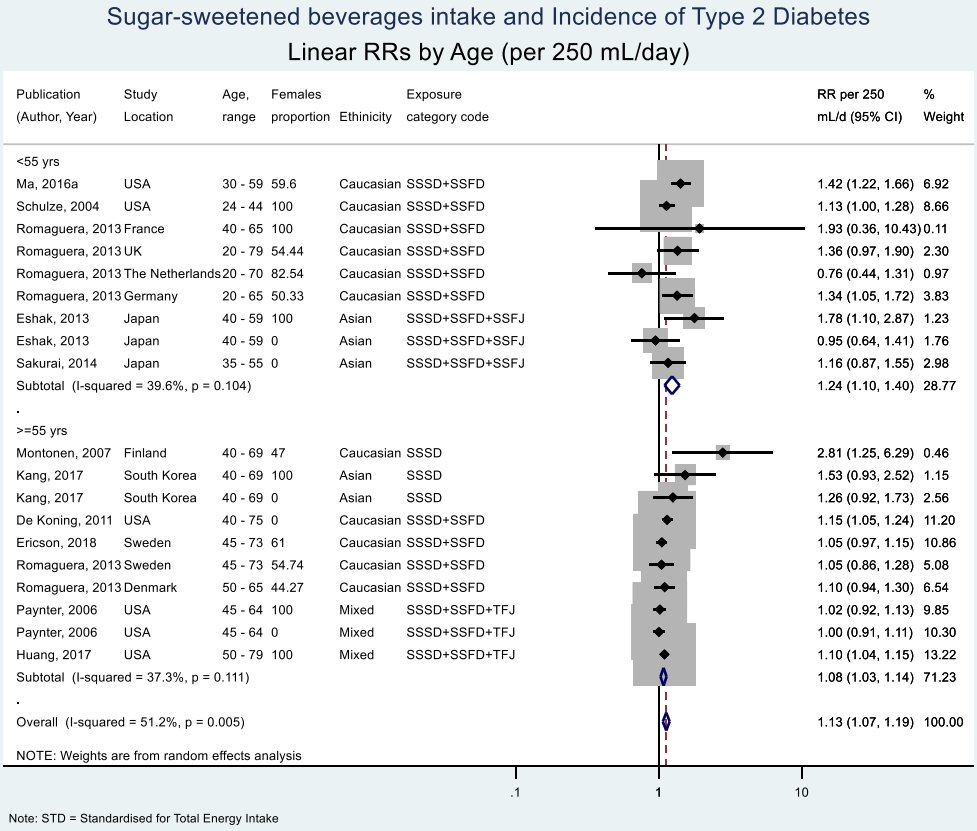


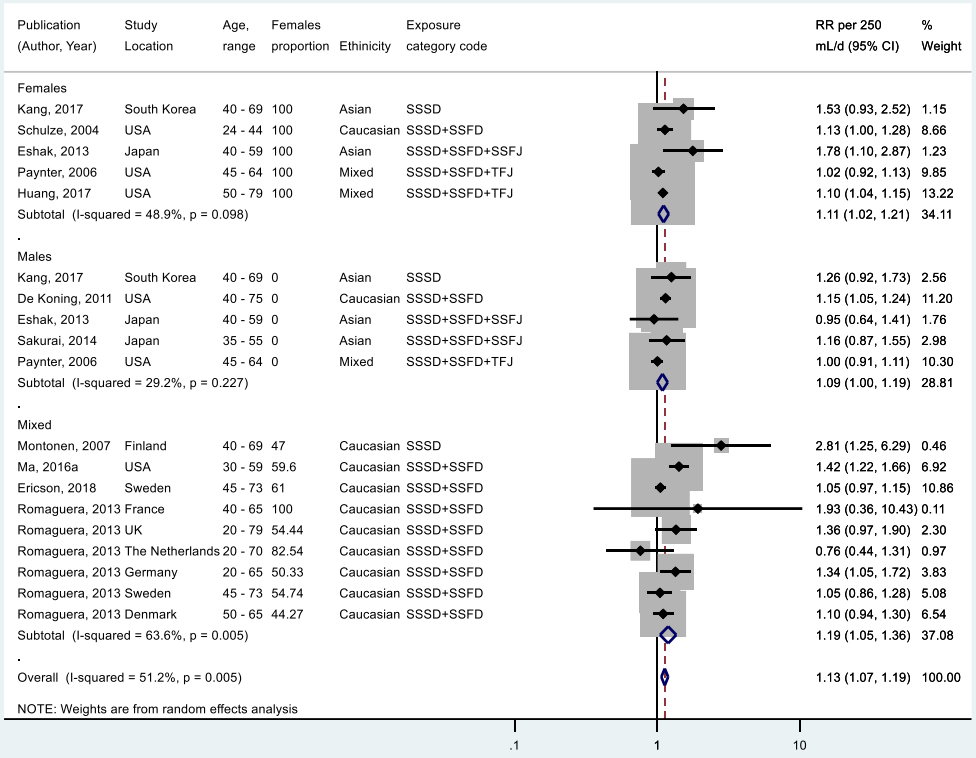
Figure C.4 Exposure scores from the SSBs and CVD dose–response meta-analysis

Appendix D – Forest plots on subgroup analyses

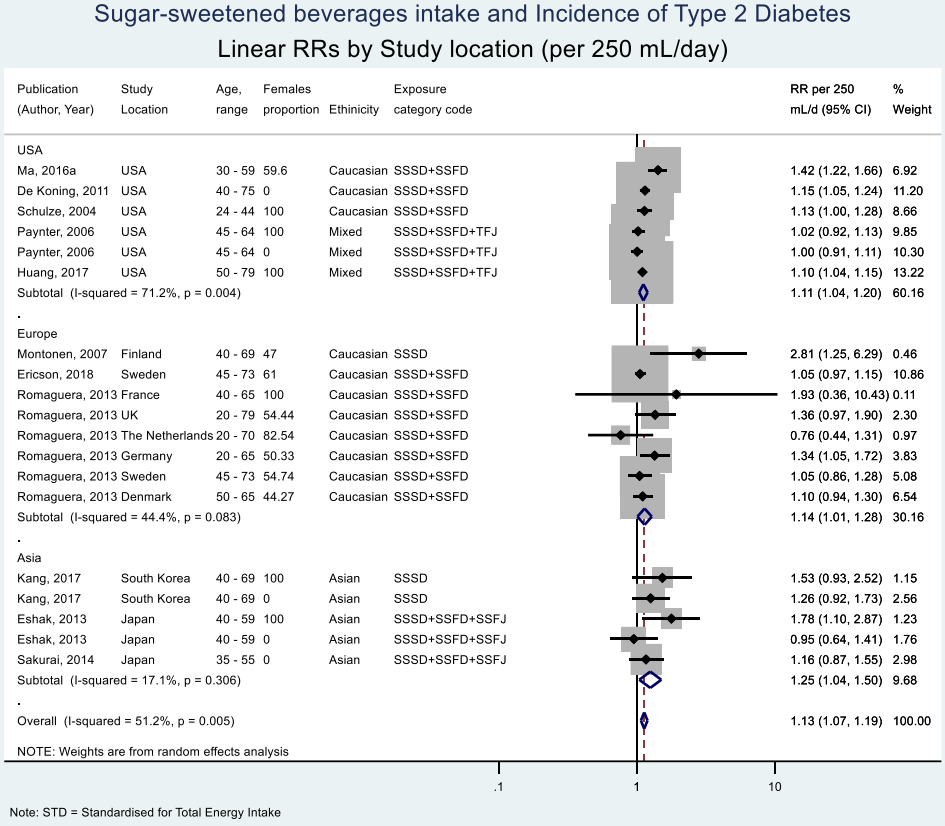


Sugar-sweetened beverages intake and Incidence of Type 2 Diabetes

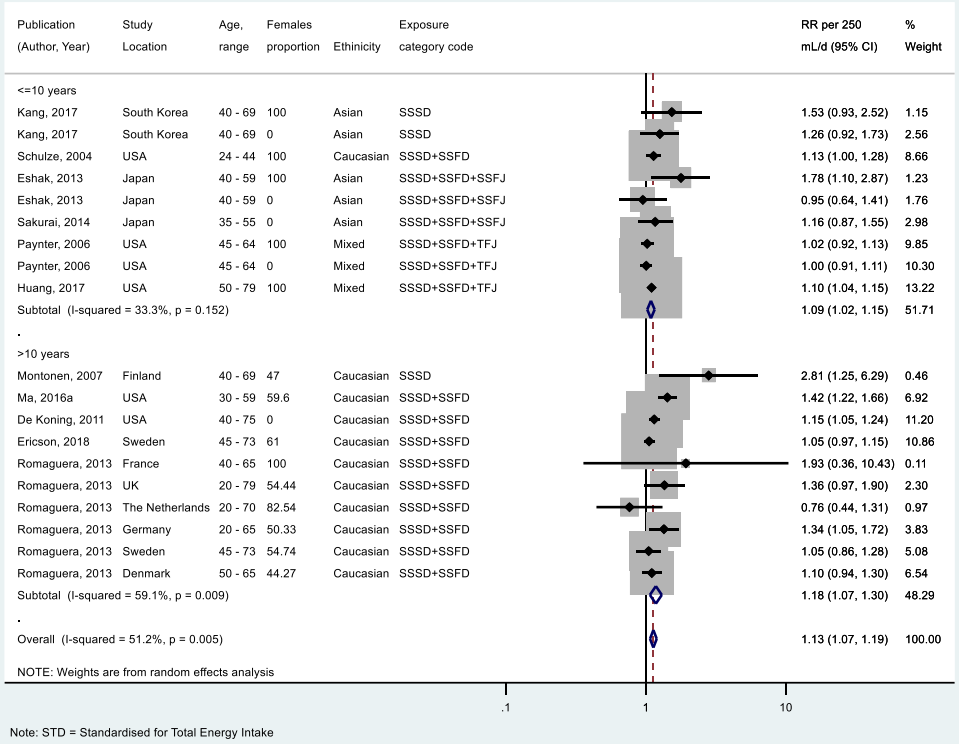
Linear RRs by sex (per 250 mL/day)



Note: STD = Standardised for Total Energy Intake



Note: STD = Standardised for Total Energy Intake


Sugar-sweetened beverages intake and Incidence of Type 2 Diabetes
Linear RRs by Follow-up time (per 250 mL/day)
Publication (Author, Year)
Study Location
Age, range
Females proportion
Ethinicity
Exposure category code
RR per 250 mL/d (95% CI)
% Weight
<=10 years
Kang, 2017 South Korea 40 - 69 100 Asian SSSD 1.53 (0.93, 2.52) 1.15
Kang, 2017 South Korea 40 - 69 0 Asian SSSD 1.26 (0.92, 1.73) 2.56
Schulze, 2004 USA 24 - 44 100 Caucasian SSSD+SSFD 1.13 (1.00, 1.28) 8.66
Eshak, 2013 Japan 40 - 59 100 Asian SSSD+SSFD+SSFJ 1.78 (1.10, 2.87) 1.23
Eshak, 2013 Japan 40 - 59 0 Asian SSSD+SSFD+SSFJ 0.95 (0.64, 1.41) 1.76
Sakurai, 2014 Japan 35 - 55 0 Asian SSSD+SSFD+SSFJ 1.16 (0.87, 1.55) 2.98
Paynter, 2006 USA 45 - 64 100 Mixed SSSD+SSFD+TFJ 1.02 (0.92, 1.13) 9.85
Paynter, 2006 USA 45 - 64 0 Mixed SSSD+SSFD+TFJ 1.00 (0.91, 1.11) 10.30
Huang, 2017 USA 50 - 79 100 Mixed SSSD+SSFD+TFJ 1.10 (1.04, 1.15) 13.22
Subtotal (I-squared = 33.3%, p = 0.152) 1.09 (1.02, 1.15) 51.71
>10 years
Montonen, 2007 Finland 40 - 69 47 Caucasian SSSD 2.81 (1.25, 6.29) 0.46
Ma, 2016a USA 30 - 59 59.6 Caucasian SSSD+SSFD 1.42 (1.22, 1.66) 6.92
De Koning, 2011 USA 40 - 75 0 Caucasian SSSD+SSFD 1.15 (1.05, 1.24) 11.20
Ericson, 2018 Sweden 45 - 73 61 Caucasian SSSD+SSFD 1.05 (0.97, 1.15) 10.86
Romaguera, 2013 France 40 - 65 100 Caucasian SSSD+SSFD 1.93 (0.36, 10.43) 0.11
Romaguera, 2013 UK 20 - 79 54.44 Caucasian SSSD+SSFD 1.36 (0.97, 1.90) 2.30
Romaguera, 2013 The Netherlands 20 - 70 82.54 Caucasian SSSD+SSFD 0.76 (0.44, 1.31) 0.97
Romaguera, 2013 Germany 20 - 65 50.33 Caucasian SSSD+SSFD 1.34 (1.05, 1.72) 3.83
Romaguera, 2013 Sweden 45 - 73 54.74 Caucasian SSSD+SSFD 1.05 (0.86, 1.28) 5.08
Romaguera, 2013 Denmark 50 - 65 44.27 Caucasian SSSD+SSFD 1.10 (0.94, 1.30) 6.54
Subtotal (I-squared = 59.1%, p = 0.009) 1.18 (1.07, 1.30) 48.29
Overall (I-squared = 51.2%, p = 0.005) 1.13 (1.07, 1.19) 100.00
NOTE: Weights are from random effects analysis
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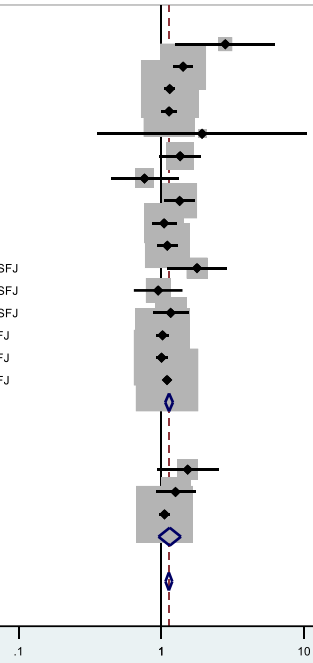
Note: STD = Standardised for Total Energy Intake

Sugar-sweetened beverages intake and Incidence of Type 2 Diabetes

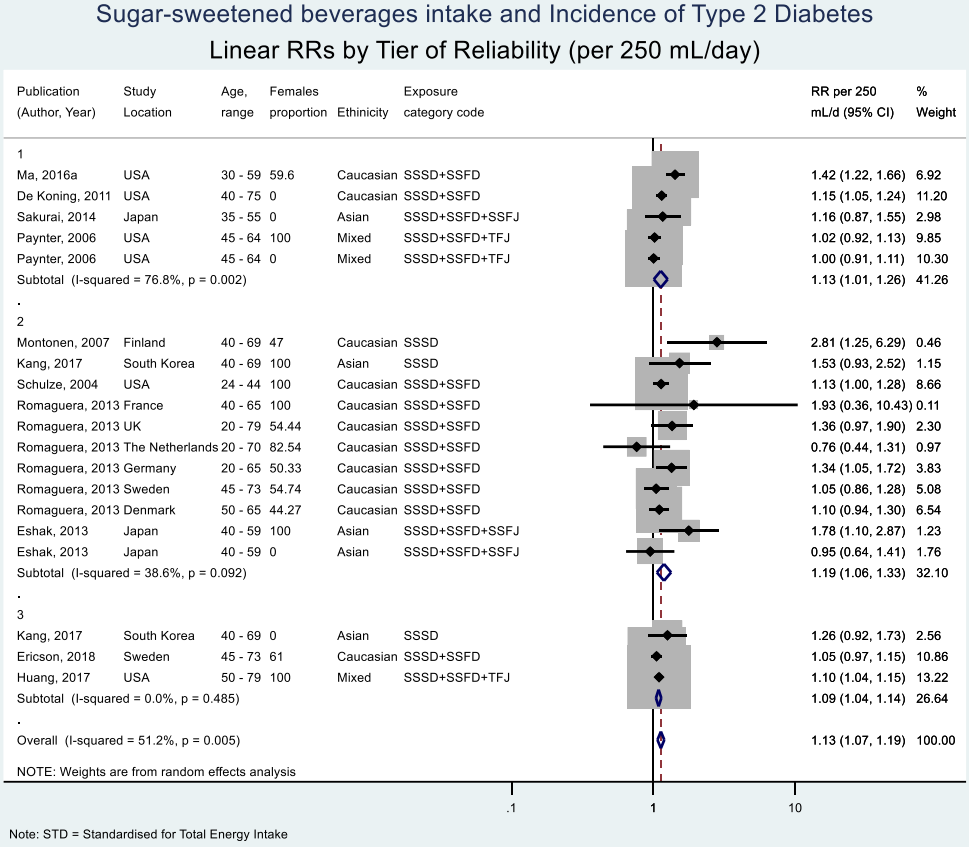
Linear RRs by Exposure categorisation (per 250 mL/day)

Publication (Author, Year)	Study Location	Age, range	Females proportion	Ethinicity	Exposure category code	RR per 250 mL/d (95% CI)	% Weight
Other referent category							
Montonen, 2007	Finland	40 - 69	47	Caucasian	SSSD	2.81 (1.25, 6.29)	0.46
Ma, 2016a	USA	30 - 59	59.6	Caucasian	SSSD+SSFD	1.42 (1.22, 1.66)	6.92
De Koning, 2011	USA	40 - 75	0	Caucasian	SSSD+SSFD	1.15 (1.05, 1.24)	11.20
Schulze, 2004	USA	24 - 44	100	Caucasian	SSSD+SSFD	1.13 (1.00, 1.28)	8.66
Romaguera, 2013	France	40 - 65	100	Caucasian	SSSD+SSFD	1.93 (0.36, 10.43)	0.11
Romaguera, 2013	UK	20 - 79	54.44	Caucasian	SSSD+SSFD	1.36 (0.97, 1.90)	2.30
Romaguera, 2013	The Netherlands	20 - 70	82.54	Caucasian	SSSD+SSFD	0.76 (0.44, 1.31)	0.97
Romaguera, 2013	Germany	20 - 65	50.33	Caucasian	SSSD+SSFD	1.34 (1.05, 1.72)	3.83
Romaguera, 2013	Sweden	45 - 73	54.74	Caucasian	SSSD+SSFD	1.05 (0.86, 1.28)	5.08
Romaguera, 2013	Denmark	50 - 65	44.27	Caucasian	SSSD+SSFD	1.10 (0.94, 1.30)	6.54
Eshak, 2013	Japan	40 - 59	100	Asian	SSSD+SSFD+SSFJ	1.78 (1.10, 2.87)	1.23
Eshak, 2013	Japan	40 - 59	0	Asian	SSSD+SSFD+SSFJ	0.95 (0.64, 1.41)	1.76
Sakurai, 2014	Japan	35 - 55	0	Asian	SSSD+SSFD+SSFJ	1.16 (0.87, 1.55)	2.98
Paynter, 2006	USA	45 - 64	100	Mixed	SSSD+SSFD+TFJ	1.02 (0.92, 1.13)	9.85
Paynter, 2006	USA	45 - 64	0	Mixed	SSSD+SSFD+TFJ	1.00 (0.91, 1.11)	10.30
Huang, 2017	USA	50 - 79	100	Mixed	SSSD+SSFD+TFJ	1.10 (1.04, 1.15)	13.22
Subtotal (I-squared = 55.1%, p = 0.004)						1.13 (1.06, 1.21)	85.43
.							
Non-consumers as referent category							
Kang, 2017	South Korea	40 - 69	100	Asian	SSSD	1.53 (0.93, 2.52)	1.15
Kang, 2017	South Korea	40 - 69	0	Asian	SSSD	1.26 (0.92, 1.73)	2.56
Ericson, 2018	Sweden	45 - 73	61	Caucasian	SSSD+SSFD	1.05 (0.97, 1.15)	10.86
Subtotal (I-squared = 35.6%, p = 0.212)						1.15 (0.96, 1.37)	14.57
.							
Overall (I-squared = 51.2%, p = 0.005)						1.13 (1.07, 1.19)	100.00

NOTE: Weights are from random effects analysis



Note: STD = Standardised for Total Energy Intake


Sugar-sweetened beverages intake and Incidence of Type 2 Diabetes
Linear RRs by Tier of Reliability (per 250 mL/day)
Publication (Author, Year) | Study Location | Age, range | Females proportion | Ethinicity | Exposure category code | RR per 250 mL/d (95% CI) | % Weight
1
Ma, 2016a USA 30 - 59 59.6 Caucasian SSSD+SSFD 1.42 (1.22, 1.66) 6.92
De Koning, 2011 USA 40 - 75 0 Caucasian SSSD+SSFD 1.15 (1.05, 1.24) 11.20
Sakurai, 2014 Japan 35 - 55 0 Asian SSSD+SSFD+SSFJ 1.16 (0.87, 1.55) 2.98
Paynter, 2006 USA 45 - 64 100 Mixed SSSD+SSFD+TFJ 1.02 (0.92, 1.13) 9.85
Paynter, 2006 USA 45 - 64 0 Mixed SSSD+SSFD+TFJ 1.00 (0.91, 1.11) 10.30
Subtotal (I-squared = 76.8%, p = 0.002) 1.13 (1.01, 1.26) 41.26
2
Montonen, 2007 Finland 40 - 69 47 Caucasian SSSD 2.81 (1.25, 6.29) 0.46
Kang, 2017 South Korea 40 - 69 100 Asian SSSD 1.53 (0.93, 2.52) 1.15
Schulze, 2004 USA 24 - 44 100 Caucasian SSSD+SSFD 1.13 (1.00, 1.28) 8.66
Romaguera, 2013 France 40 - 65 100 Caucasian SSSD+SSFD 1.93 (0.36, 10.43) 0.11
Romaguera, 2013 UK 20 - 79 54.44 Caucasian SSSD+SSFD 1.36 (0.97, 1.90) 2.30
Romaguera, 2013 The Netherlands 20 - 70 82.54 Caucasian SSSD+SSFD 0.76 (0.44, 1.31) 0.97
Romaguera, 2013 Germany 20 - 65 50.33 Caucasian SSSD+SSFD 1.34 (1.05, 1.72) 3.83
Romaguera, 2013 Sweden 45 - 73 54.74 Caucasian SSSD+SSFD 1.05 (0.86, 1.28) 5.08
Romaguera, 2013 Denmark 50 - 65 44.27 Caucasian SSSD+SSFD 1.10 (0.94, 1.30) 6.54
Eshak, 2013 Japan 40 - 59 100 Asian SSSD+SSFD+SSFJ 1.78 (1.10, 2.87) 1.23
Eshak, 2013 Japan 40 - 59 0 Asian SSSD+SSFD+SSFJ 0.95 (0.64, 1.41) 1.76
Subtotal (I-squared = 38.6%, p = 0.092) 1.19 (1.06, 1.33) 32.10
3
Kang, 2017 South Korea 40 - 69 0 Asian SSSD 1.26 (0.92, 1.73) 2.56
Ericson, 2018 Sweden 45 - 73 61 Caucasian SSSD+SSFD 1.05 (0.97, 1.15) 10.86
Huang, 2017 USA 50 - 79 100 Mixed SSSD+SSFD+TFJ 1.10 (1.04, 1.15) 13.22
Subtotal (I-squared = 0.0%, p = 0.485) 1.09 (1.04, 1.14) 26.64
Overall (I-squared = 51.2%, p = 0.005) 1.13 (1.07, 1.19) 100.00
NOTE: Weights are from random effects analysis
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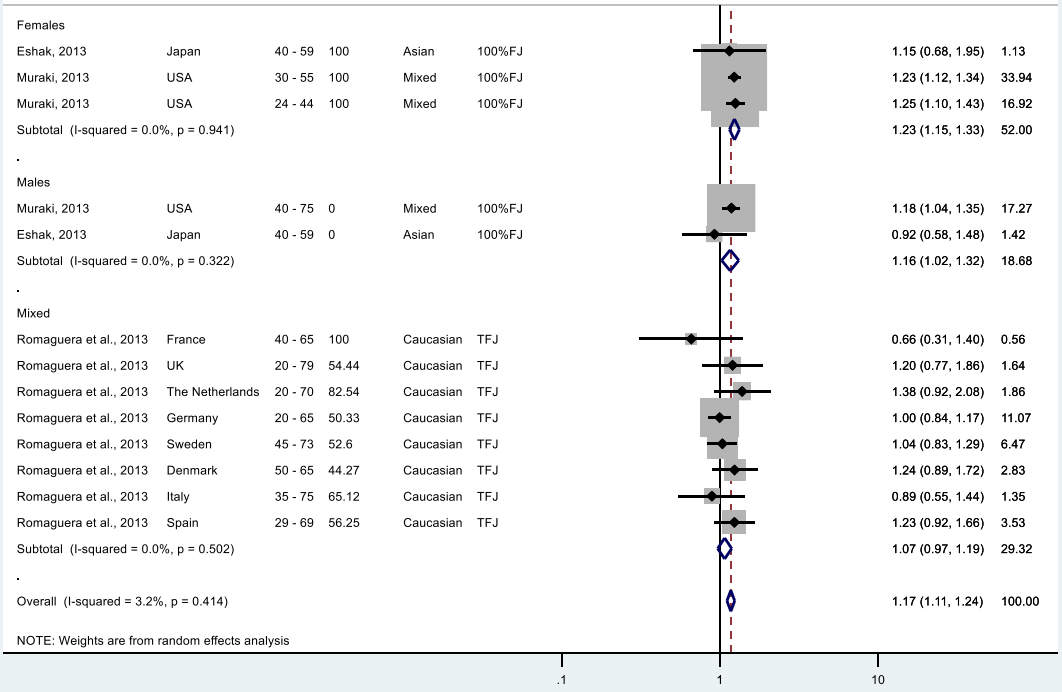
Note: STD = Standardised for Total Energy Intake

Fruit juices intake and Incidence of Type 2 Diabetes

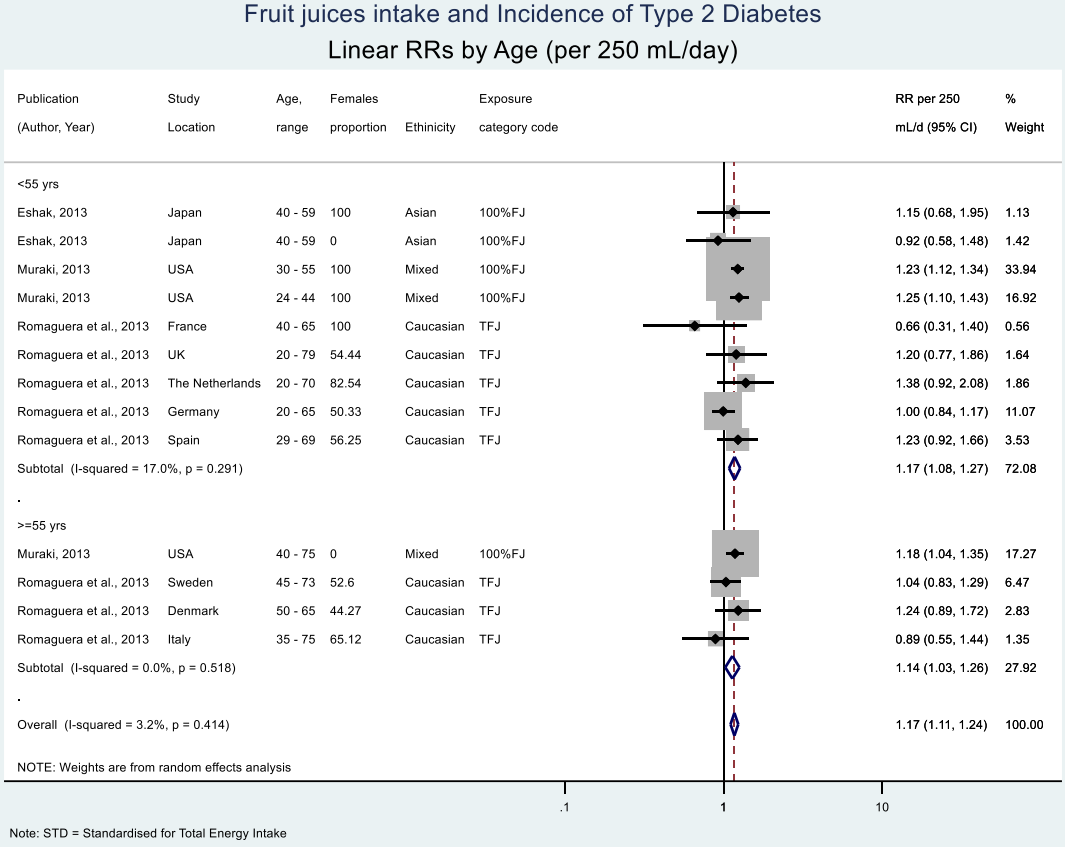
Linear RRs by sex (per 250 mL/day)

Publication (Author, Year)	Study Location	Age, range	Females proportion	Ethinicity	Exposure category code	RR per 250 mL/d (95% CI)	% Weight
Females							
Eshak, 2013	Japan	40 - 59	100	Asian	100%FJ	1.15 (0.68, 1.95)	1.13
Muraki, 2013	USA	30 - 55	100	Mixed	100%FJ	1.23 (1.12, 1.34)	33.94
Muraki, 2013	USA	24 - 44	100	Mixed	100%FJ	1.25 (1.10, 1.43)	16.92
Subtotal (I-squared = 0.0%, p = 0.941)						1.23 (1.15, 1.33)	52.00
.							
Males							
Muraki, 2013	USA	40 - 75	0	Mixed	100%FJ	1.18 (1.04, 1.35)	17.27
Eshak, 2013	Japan	40 - 59	0	Asian	100%FJ	0.92 (0.58, 1.48)	1.42
Subtotal (I-squared = 0.0%, p = 0.322)						1.16 (1.02, 1.32)	18.68
.							
Mixed							
Romaguera et al., 2013	France	40 - 65	100	Caucasian	TFJ	0.66 (0.31, 1.40)	0.56
Romaguera et al., 2013	UK	20 - 79	54.44	Caucasian	TFJ	1.20 (0.77, 1.86)	1.64
Romaguera et al., 2013	The Netherlands	20 - 70	82.54	Caucasian	TFJ	1.38 (0.92, 2.08)	1.86
Romaguera et al., 2013	Germany	20 - 65	50.33	Caucasian	TFJ	1.00 (0.84, 1.17)	11.07
Romaguera et al., 2013	Sweden	45 - 73	52.6	Caucasian	TFJ	1.04 (0.83, 1.29)	6.47
Romaguera et al., 2013	Denmark	50 - 65	44.27	Caucasian	TFJ	1.24 (0.89, 1.72)	2.83
Romaguera et al., 2013	Italy	35 - 75	65.12	Caucasian	TFJ	0.89 (0.55, 1.44)	1.35
Romaguera et al., 2013	Spain	29 - 69	56.25	Caucasian	TFJ	1.23 (0.92, 1.66)	3.53
Subtotal (I-squared = 0.0%, p = 0.502)						1.07 (0.97, 1.19)	29.32
.							
Overall (I-squared = 3.2%, p = 0.414)						1.17 (1.11, 1.24)	100.00

NOTE: Weights are from random effects analysis



Note: STD = Standardised for Total Energy Intake


Fruit juices intake and Incidence of Type 2 Diabetes
Linear RRs by Age (per 250 mL/day)
Publication (Author, Year)
Study Location
Age, range
Females proportion
Ethinicity
Exposure category code
RR per 250 mL/d (95% CI)
% Weight
<55 yrs
Eshak, 2013 Japan 40 - 59 100 Asian 100%FJ 1.15 (0.68, 1.95) 1.13
Eshak, 2013 Japan 40 - 59 0 Asian 100%FJ 0.92 (0.58, 1.48) 1.42
Muraki, 2013 USA 30 - 55 100 Mixed 100%FJ 1.23 (1.12, 1.34) 33.94
Muraki, 2013 USA 24 - 44 100 Mixed 100%FJ 1.25 (1.10, 1.43) 16.92
Romaguera et al., 2013 France 40 - 65 100 Caucasian TFJ 0.66 (0.31, 1.40) 0.56
Romaguera et al., 2013 UK 20 - 79 54.44 Caucasian TFJ 1.20 (0.77, 1.86) 1.64
Romaguera et al., 2013 The Netherlands 20 - 70 82.54 Caucasian TFJ 1.38 (0.92, 2.08) 1.86
Romaguera et al., 2013 Germany 20 - 65 50.33 Caucasian TFJ 1.00 (0.84, 1.17) 11.07
Romaguera et al., 2013 Spain 29 - 69 56.25 Caucasian TFJ 1.23 (0.92, 1.66) 3.53
Subtotal (I-squared = 17.0%, p = 0.291) 1.17 (1.08, 1.27) 72.08
.
>=55 yrs
Muraki, 2013 USA 40 - 75 0 Mixed 100%FJ 1.18 (1.04, 1.35) 17.27
Romaguera et al., 2013 Sweden 45 - 73 52.6 Caucasian TFJ 1.04 (0.83, 1.29) 6.47
Romaguera et al., 2013 Denmark 50 - 65 44.27 Caucasian TFJ 1.24 (0.89, 1.72) 2.83
Romaguera et al., 2013 Italy 35 - 75 65.12 Caucasian TFJ 0.89 (0.55, 1.44) 1.35
Subtotal (I-squared = 0.0%, p = 0.518) 1.14 (1.03, 1.26) 27.92
.
Overall (I-squared = 3.2%, p = 0.414) 1.17 (1.11, 1.24) 100.00
NOTE: Weights are from random effects analysis
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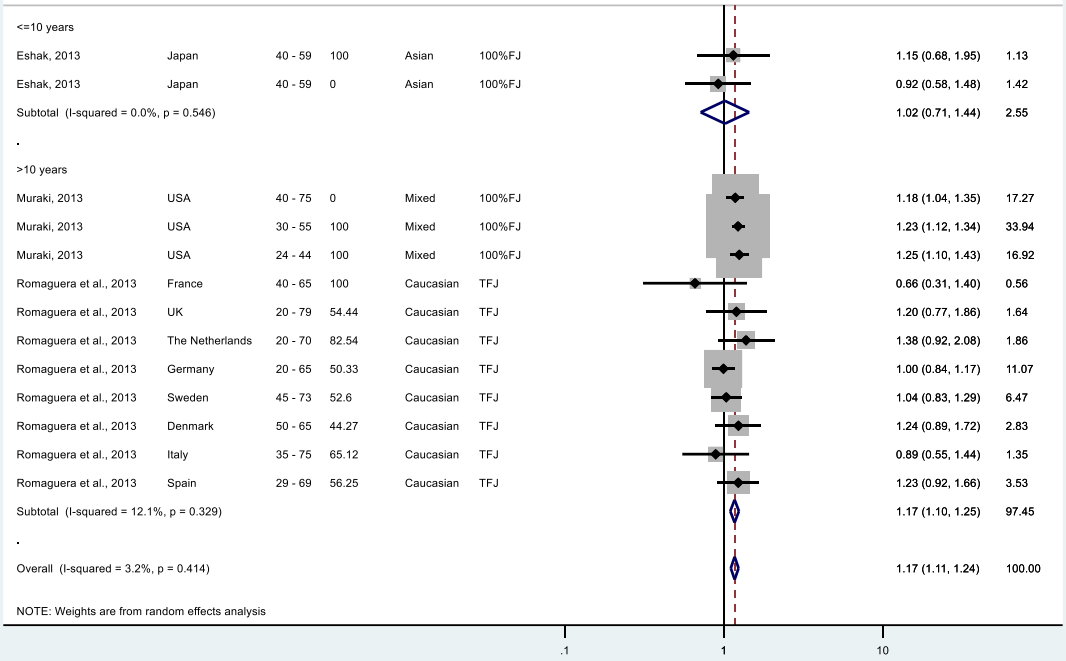
Note: STD = Standardised for Total Energy Intake

Fruit juices intake and Incidence of Type 2 Diabetes

Linear RRs by Follow-up time (per 250 mL/day)

Publication (Author, Year)	Study Location	Age, range	Females proportion	Ethinicity	Exposure category code	RR per 250 mL/d (95% CI)	% Weight
<=10 years							
Eshak, 2013	Japan	40 - 59	100	Asian	100%FJ	1.15 (0.68, 1.95)	1.13
Eshak, 2013	Japan	40 - 59	0	Asian	100%FJ	0.92 (0.58, 1.48)	1.42
Subtotal (I-squared = 0.0%, p = 0.546)						1.02 (0.71, 1.44)	2.55
.							
>10 years							
Muraki, 2013	USA	40 - 75	0	Mixed	100%FJ	1.18 (1.04, 1.35)	17.27
Muraki, 2013	USA	30 - 55	100	Mixed	100%FJ	1.23 (1.12, 1.34)	33.94
Muraki, 2013	USA	24 - 44	100	Mixed	100%FJ	1.25 (1.10, 1.43)	16.92
Romaguera et al., 2013	France	40 - 65	100	Caucasian	TFJ	0.66 (0.31, 1.40)	0.56
Romaguera et al., 2013	UK	20 - 79	54.44	Caucasian	TFJ	1.20 (0.77, 1.86)	1.64
Romaguera et al., 2013	The Netherlands	20 - 70	82.54	Caucasian	TFJ	1.38 (0.92, 2.08)	1.86
Romaguera et al., 2013	Germany	20 - 65	50.33	Caucasian	TFJ	1.00 (0.84, 1.17)	11.07
Romaguera et al., 2013	Sweden	45 - 73	52.6	Caucasian	TFJ	1.04 (0.83, 1.29)	6.47
Romaguera et al., 2013	Denmark	50 - 65	44.27	Caucasian	TFJ	1.24 (0.89, 1.72)	2.83
Romaguera et al., 2013	Italy	35 - 75	65.12	Caucasian	TFJ	0.89 (0.55, 1.44)	1.35
Romaguera et al., 2013	Spain	29 - 69	56.25	Caucasian	TFJ	1.23 (0.92, 1.66)	3.53
Subtotal (I-squared = 12.1%, p = 0.329)						1.17 (1.10, 1.25)	97.45
.							
Overall (I-squared = 3.2%, p = 0.414)						1.17 (1.11, 1.24)	100.00

NOTE: Weights are from random effects analysis



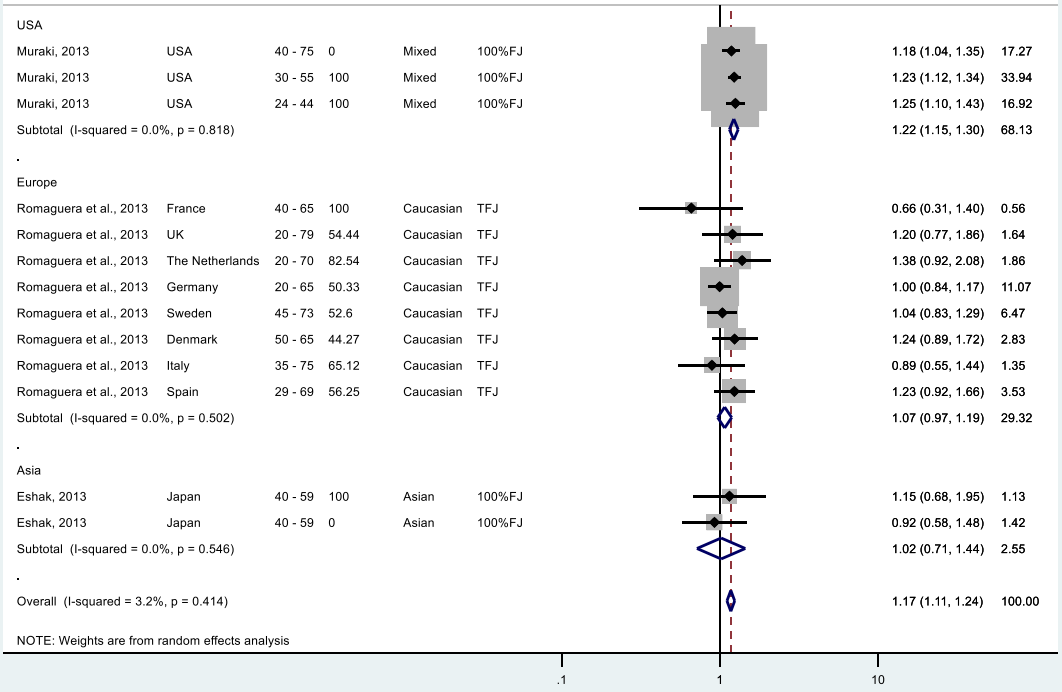
Note: STD = Standardised for Total Energy Intake

Fruit juices intake and Incidence of Type 2 Diabetes

Linear RRs by Study location (per 250 mL/day)

Publication (Author, Year)	Study Location	Age, range	Females proportion	Ethinicity	Exposure category code	RR per 250 mL/d (95% CI)	% Weight
USA							
Muraki, 2013	USA	40 - 75	0	Mixed	100%FJ	1.18 (1.04, 1.35)	17.27
Muraki, 2013	USA	30 - 55	100	Mixed	100%FJ	1.23 (1.12, 1.34)	33.94
Muraki, 2013	USA	24 - 44	100	Mixed	100%FJ	1.25 (1.10, 1.43)	16.92
Subtotal (I-squared = 0.0%, p = 0.818)						1.22 (1.15, 1.30)	68.13
.							
Europe							
Romaguera et al., 2013	France	40 - 65	100	Caucasian	TFJ	0.66 (0.31, 1.40)	0.56
Romaguera et al., 2013	UK	20 - 79	54.44	Caucasian	TFJ	1.20 (0.77, 1.86)	1.64
Romaguera et al., 2013	The Netherlands	20 - 70	82.54	Caucasian	TFJ	1.38 (0.92, 2.08)	1.86
Romaguera et al., 2013	Germany	20 - 65	50.33	Caucasian	TFJ	1.00 (0.84, 1.17)	11.07
Romaguera et al., 2013	Sweden	45 - 73	52.6	Caucasian	TFJ	1.04 (0.83, 1.29)	6.47
Romaguera et al., 2013	Denmark	50 - 65	44.27	Caucasian	TFJ	1.24 (0.89, 1.72)	2.83
Romaguera et al., 2013	Italy	35 - 75	65.12	Caucasian	TFJ	0.89 (0.55, 1.44)	1.35
Romaguera et al., 2013	Spain	29 - 69	56.25	Caucasian	TFJ	1.23 (0.92, 1.66)	3.53
Subtotal (I-squared = 0.0%, p = 0.502)						1.07 (0.97, 1.19)	29.32
.							
Asia							
Eshak, 2013	Japan	40 - 59	100	Asian	100%FJ	1.15 (0.68, 1.95)	1.13
Eshak, 2013	Japan	40 - 59	0	Asian	100%FJ	0.92 (0.58, 1.48)	1.42
Subtotal (I-squared = 0.0%, p = 0.546)						1.02 (0.71, 1.44)	2.55
.							
Overall (I-squared = 3.2%, p = 0.414)						1.17 (1.11, 1.24)	100.00

NOTE: Weights are from random effects analysis

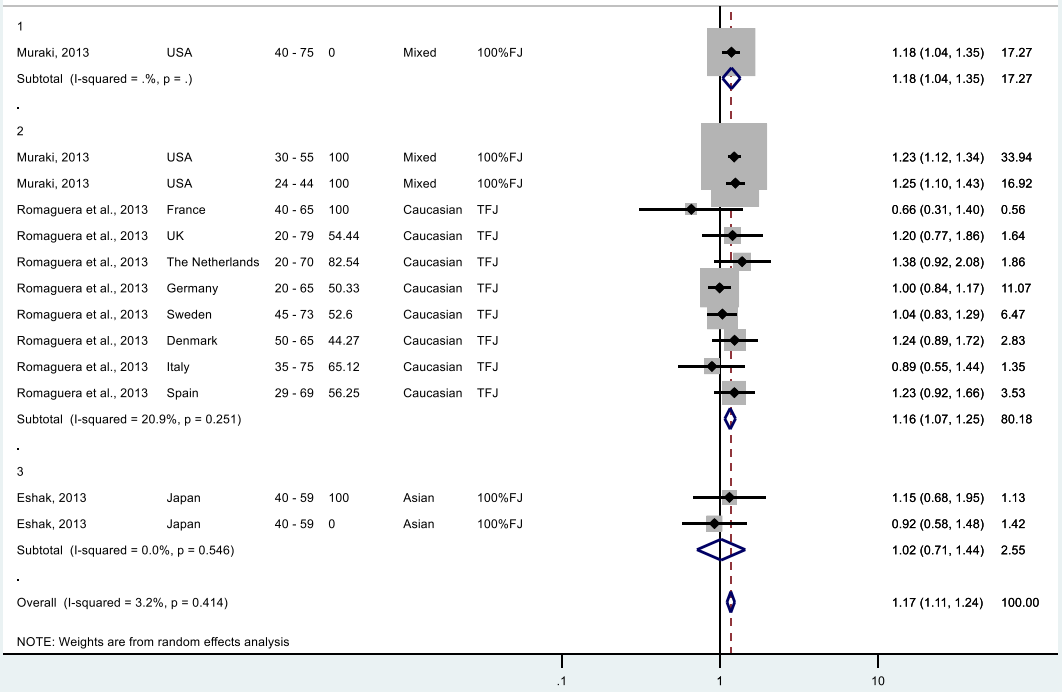


Note: STD = Standardised for Total Energy Intake

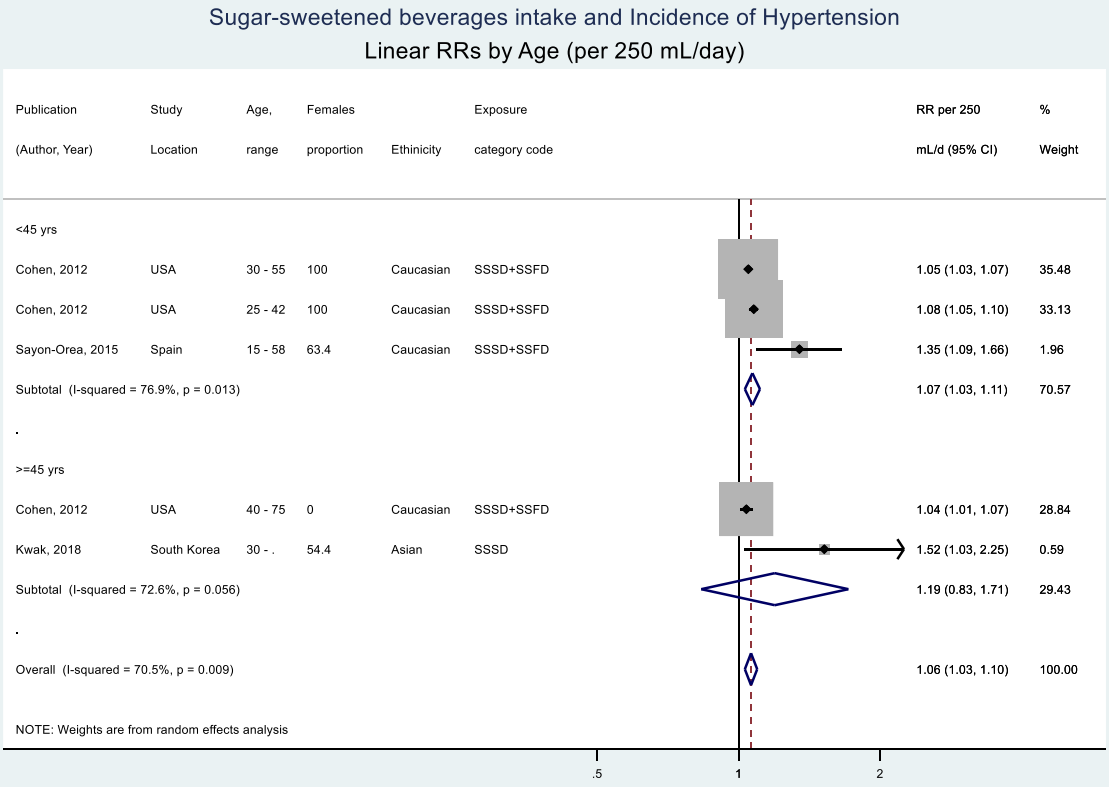
Fruit juices intake and Incidence of Type 2 Diabetes
Linear RRs by Tier of Reliability (per 250 mL/day)

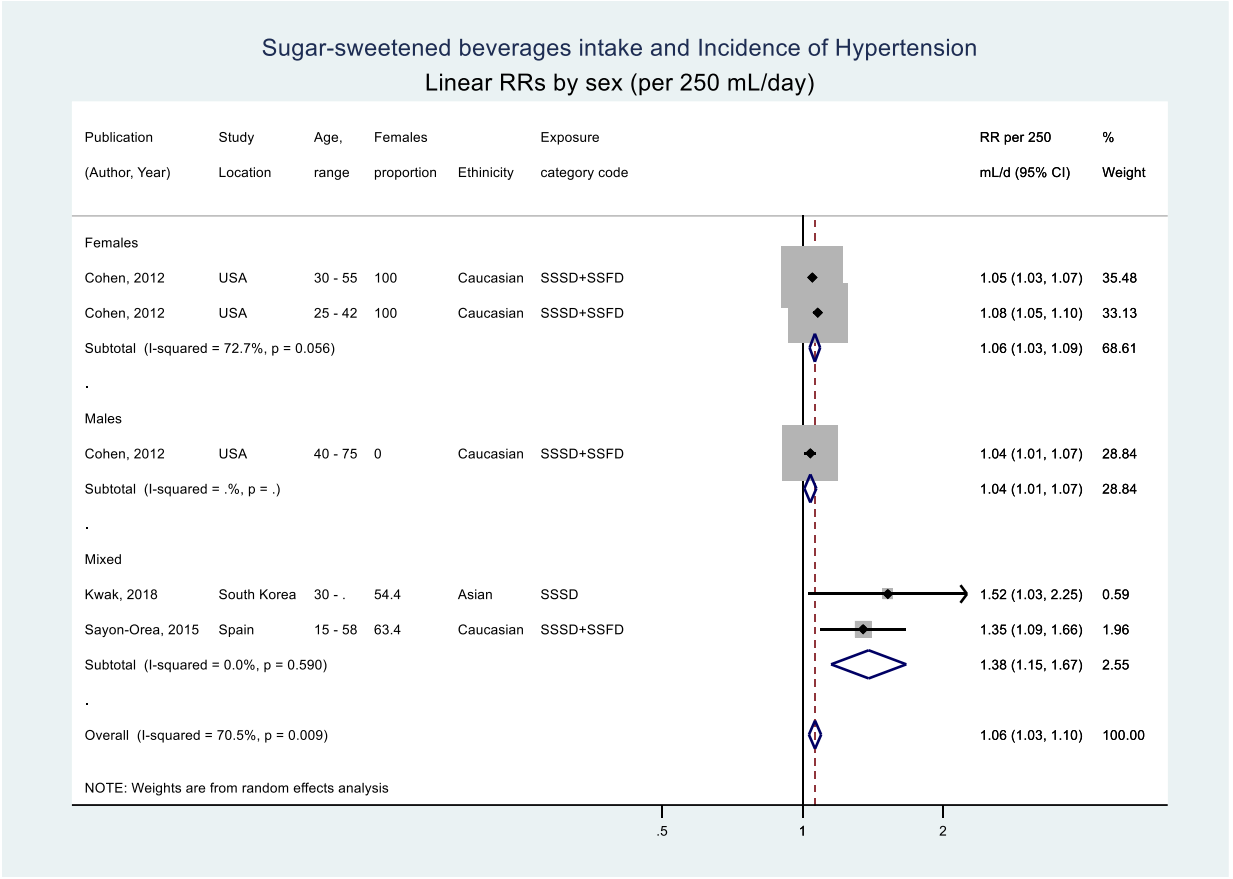
Publication (Author, Year)	Study Location	Age, range	Females proportion	Ethinicity	Exposure category code	RR per 250 mL/d (95% CI)	% Weight
1							
Muraki, 2013	USA	40 - 75	0	Mixed	100%FJ	1.18 (1.04, 1.35)	17.27
Subtotal (I-squared = .%, p = .)						1.18 (1.04, 1.35)	17.27
.							
2							
Muraki, 2013	USA	30 - 55	100	Mixed	100%FJ	1.23 (1.12, 1.34)	33.94
Muraki, 2013	USA	24 - 44	100	Mixed	100%FJ	1.25 (1.10, 1.43)	16.92
Romaguera et al., 2013	France	40 - 65	100	Caucasian	TFJ	0.66 (0.31, 1.40)	0.56
Romaguera et al., 2013	UK	20 - 79	54.44	Caucasian	TFJ	1.20 (0.77, 1.86)	1.64
Romaguera et al., 2013	The Netherlands	20 - 70	82.54	Caucasian	TFJ	1.38 (0.92, 2.08)	1.86
Romaguera et al., 2013	Germany	20 - 65	50.33	Caucasian	TFJ	1.00 (0.84, 1.17)	11.07
Romaguera et al., 2013	Sweden	45 - 73	52.6	Caucasian	TFJ	1.04 (0.83, 1.29)	6.47
Romaguera et al., 2013	Denmark	50 - 65	44.27	Caucasian	TFJ	1.24 (0.89, 1.72)	2.83
Romaguera et al., 2013	Italy	35 - 75	65.12	Caucasian	TFJ	0.89 (0.55, 1.44)	1.35
Romaguera et al., 2013	Spain	29 - 69	56.25	Caucasian	TFJ	1.23 (0.92, 1.66)	3.53
Subtotal (I-squared = 20.9%, p = 0.251)						1.16 (1.07, 1.25)	80.18
.							
3							
Eshak, 2013	Japan	40 - 59	100	Asian	100%FJ	1.15 (0.68, 1.95)	1.13
Eshak, 2013	Japan	40 - 59	0	Asian	100%FJ	0.92 (0.58, 1.48)	1.42
Subtotal (I-squared = 0.0%, p = 0.546)						1.02 (0.71, 1.44)	2.55
.							
Overall (I-squared = 3.2%, p = 0.414)						1.17 (1.11, 1.24)	100.00

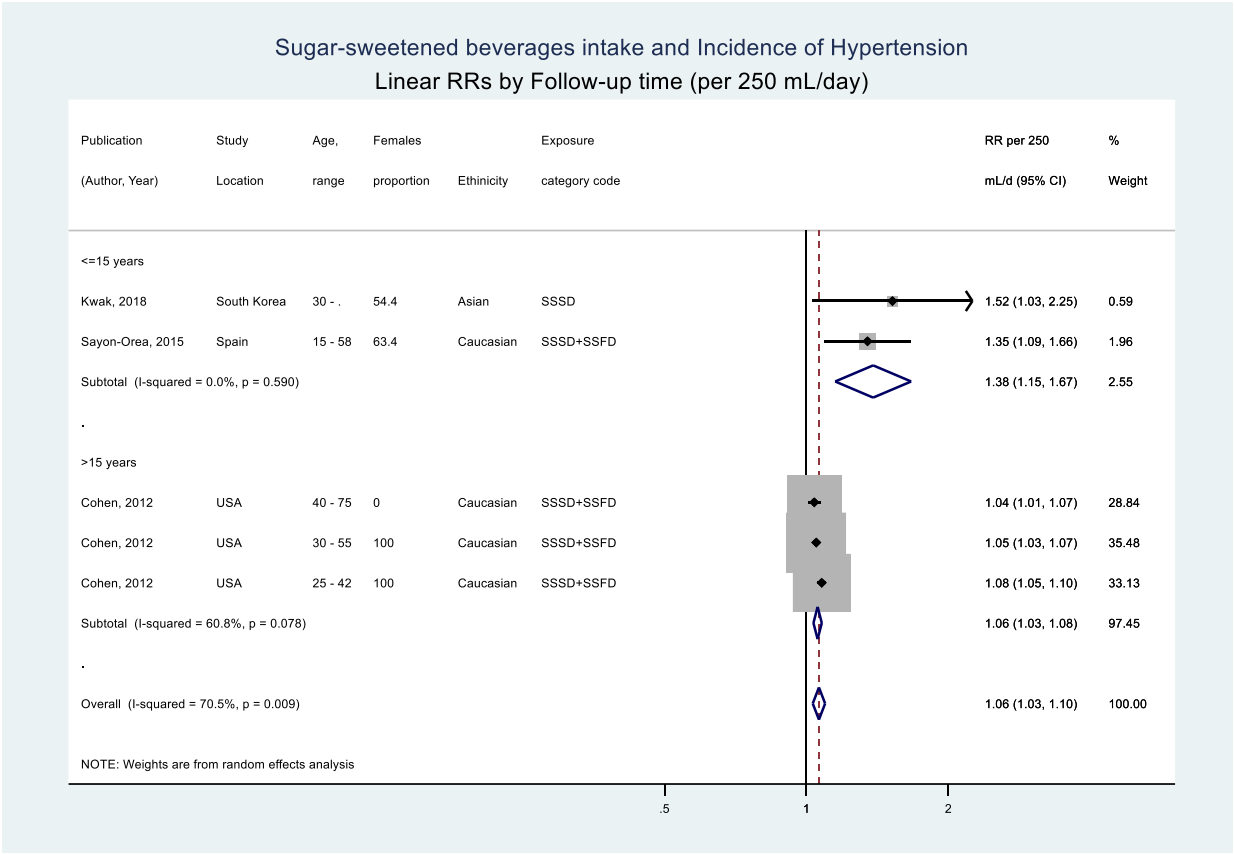
NOTE: Weights are from random effects analysis



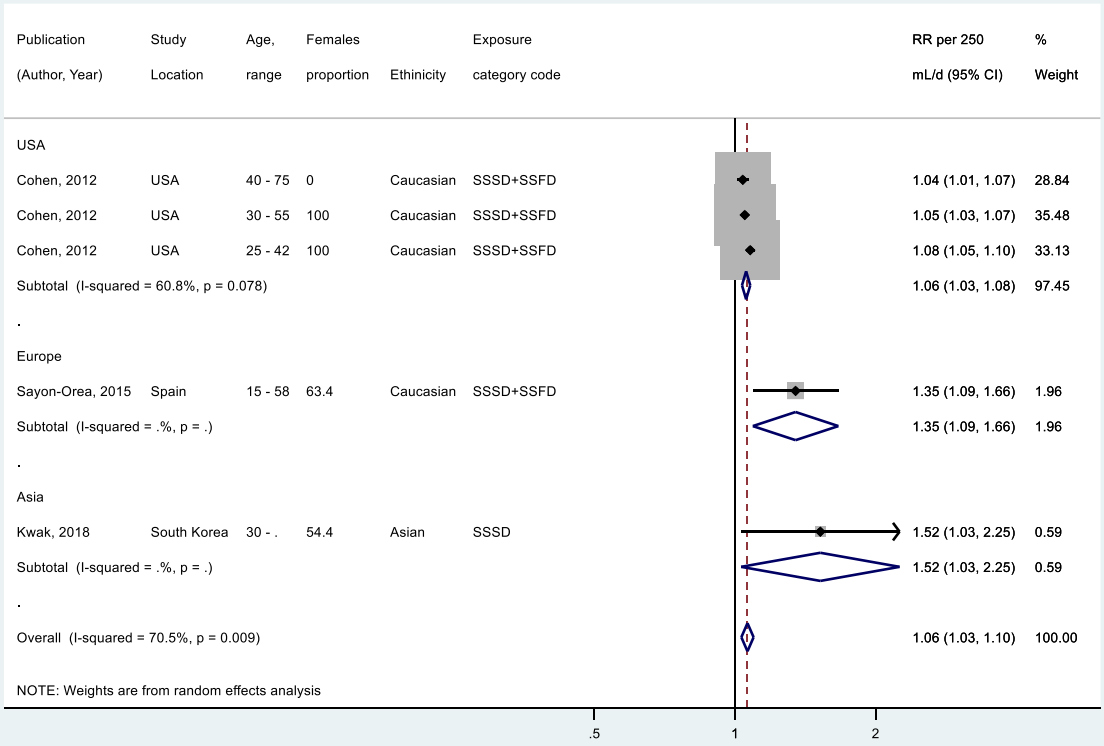
Note: STD = Standardised for Total Energy Intake

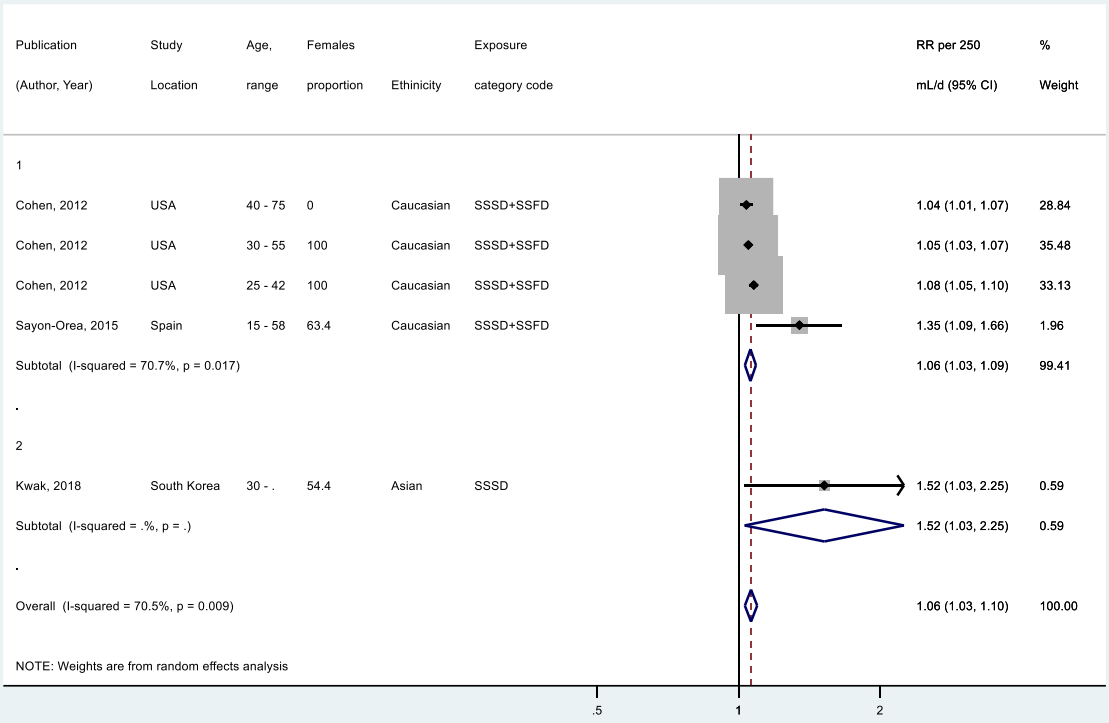

Sugar-sweetened beverages intake and Incidence of Hypertension
Linear RRs by Age (per 250 mL/day)
Publication (Author, Year)
Study Location
Age, range
Females proportion
Ethinicity
Exposure category code
RR per 250 mL/d (95% CI)
% Weight
<45 yrs
Cohen, 2012 USA 30 - 55 100 Caucasian SSSD+SSFD 1.05 (1.03, 1.07) 35.48
Cohen, 2012 USA 25 - 42 100 Caucasian SSSD+SSFD 1.08 (1.05, 1.10) 33.13
Sayon-Orea, 2015 Spain 15 - 58 63.4 Caucasian SSSD+SSFD 1.35 (1.09, 1.66) 1.96
Subtotal (I-squared = 76.9%, p = 0.013) 1.07 (1.03, 1.11) 70.57
.
>=45 yrs
Cohen, 2012 USA 40 - 75 0 Caucasian SSSD+SSFD 1.04 (1.01, 1.07) 28.84
Kwak, 2018 South Korea 30 - . 54.4 Asian SSSD 1.52 (1.03, 2.25) 0.59
Subtotal (I-squared = 72.6%, p = 0.056) 1.19 (0.83, 1.71) 29.43
.
Overall (I-squared = 70.5%, p = 0.009) 1.06 (1.03, 1.10) 100.00
NOTE: Weights are from random effects analysis
.5
1
2

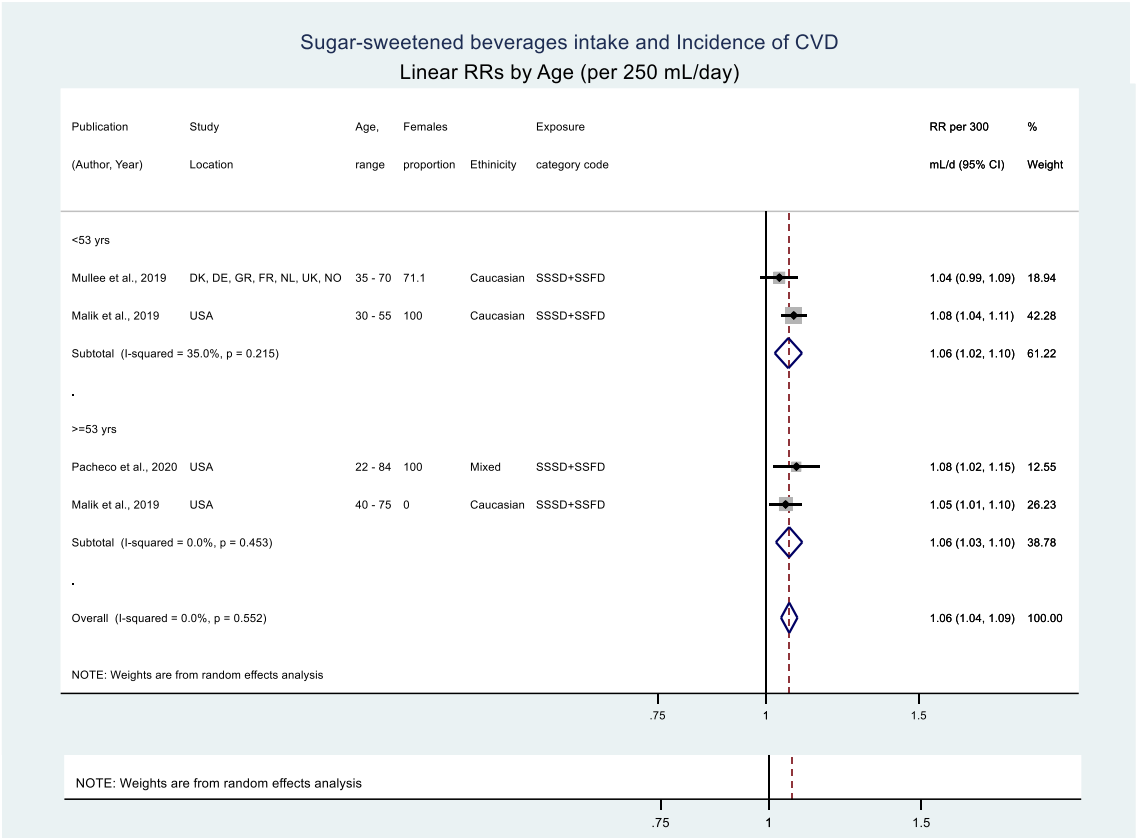

Sugar-sweetened beverages intake and Incidence of Hypertension
Linear RRs by sex (per 250 mL/day)
Publication (Author, Year)
Study Location
Age, range
Females proportion
Ethinicity
Exposure category code
RR per 250 mL/d (95% CI)
% Weight
Females
Cohen, 2012 USA 30 - 55 100 Caucasian SSSD+SSFD 1.05 (1.03, 1.07) 35.48
Cohen, 2012 USA 25 - 42 100 Caucasian SSSD+SSFD 1.08 (1.05, 1.10) 33.13
Subtotal (I-squared = 72.7%, p = 0.056) 1.06 (1.03, 1.09) 68.61
.
Males
Cohen, 2012 USA 40 - 75 0 Caucasian SSSD+SSFD 1.04 (1.01, 1.07) 28.84
Subtotal (I-squared = .%, p = .) 1.04 (1.01, 1.07) 28.84
.
Mixed
Kwak, 2018 South Korea 30 - . 54.4 Asian SSSD 1.52 (1.03, 2.25) 0.59
Sayon-Orea, 2015 Spain 15 - 58 63.4 Caucasian SSSD+SSFD 1.35 (1.09, 1.66) 1.96
Subtotal (I-squared = 0.0%, p = 0.590) 1.38 (1.15, 1.67) 2.55
.
Overall (I-squared = 70.5%, p = 0.009) 1.06 (1.03, 1.10) 100.00
NOTE: Weights are from random effects analysis
.5
1
2


Sugar-sweetened beverages intake and Incidence of Hypertension
Linear RRs by Follow-up time (per 250 mL/day)
Publication (Author, Year)
Study Location
Age, range
Females proportion
Ethinicity
Exposure category code
RR per 250 mL/d (95% CI)
% Weight
<=15 years
Kwak, 2018 South Korea 30 - . 54.4 Asian SSSD 1.52 (1.03, 2.25) 0.59
Sayon-Orea, 2015 Spain 15 - 58 63.4 Caucasian SSSD+SSFD 1.35 (1.09, 1.66) 1.96
Subtotal (I-squared = 0.0%, p = 0.590) 1.38 (1.15, 1.67) 2.55
.
>15 years
Cohen, 2012 USA 40 - 75 0 Caucasian SSSD+SSFD 1.04 (1.01, 1.07) 28.84
Cohen, 2012 USA 30 - 55 100 Caucasian SSSD+SSFD 1.05 (1.03, 1.07) 35.48
Cohen, 2012 USA 25 - 42 100 Caucasian SSSD+SSFD 1.08 (1.05, 1.10) 33.13
Subtotal (I-squared = 60.8%, p = 0.078) 1.06 (1.03, 1.08) 97.45
.
Overall (I-squared = 70.5%, p = 0.009) 1.06 (1.03, 1.10) 100.00
NOTE: Weights are from random effects analysis
.5
1
2

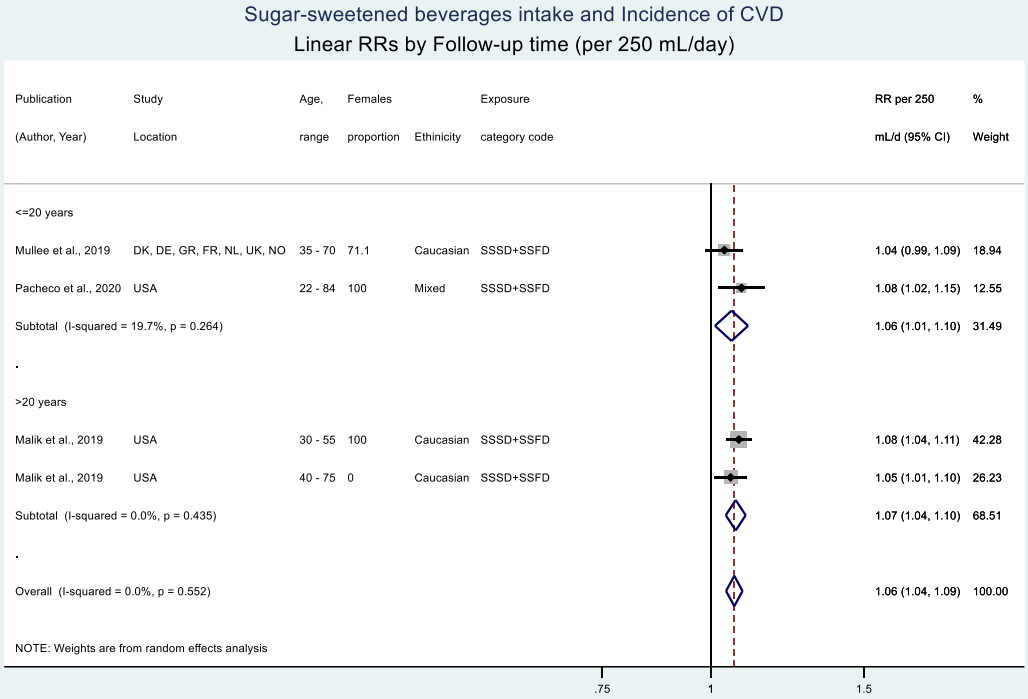
Sugar-sweetened beverages intake and Incidence of Hypertension
Linear RRs by Study location (per 250 mL/day)

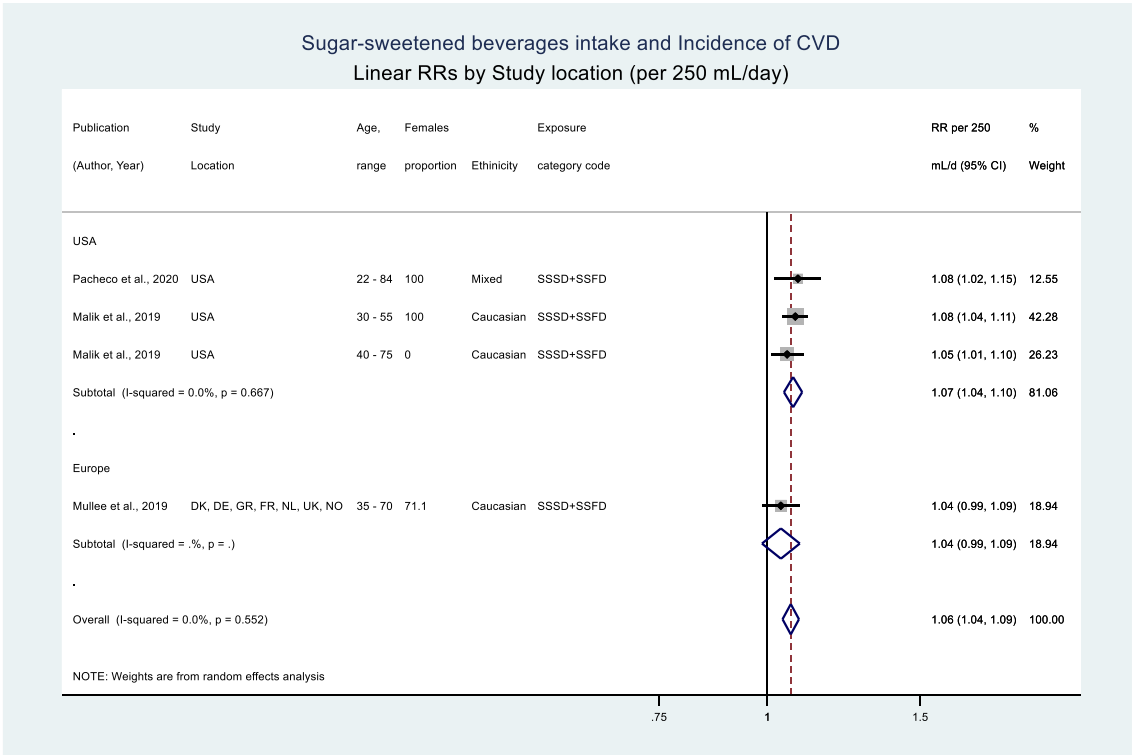



Sugar-sweetened beverages intake and Incidence of Hypertension
Linear RRs by Tier of Reliability (per 250 mL/day)
Publication (Author, Year)
Study Location
Age, range
Females proportion
Ethinicity
Exposure category code
RR per 250 mL/d (95% CI)
% Weight
1
Cohen, 2012 USA 40 - 75 0 Caucasian SSSD+SSFD 1.04 (1.01, 1.07) 28.84
Cohen, 2012 USA 30 - 55 100 Caucasian SSSD+SSFD 1.05 (1.03, 1.07) 35.48
Cohen, 2012 USA 25 - 42 100 Caucasian SSSD+SSFD 1.08 (1.05, 1.10) 33.13
Sayon-Orea, 2015 Spain 15 - 58 63.4 Caucasian SSSD+SSFD 1.35 (1.09, 1.66) 1.96
Subtotal (I-squared = 70.7%, p = 0.017) 1.06 (1.03, 1.09) 99.41
.
2
Kwak, 2018 South Korea 30 - . 54.4 Asian SSSD 1.52 (1.03, 2.25) 0.59
Subtotal (I-squared = .%, p = .) 1.52 (1.03, 2.25) 0.59
.
Overall (I-squared = 70.5%, p = 0.009) 1.06 (1.03, 1.10) 100.00
NOTE: Weights are from random effects analysis
.5
1
2

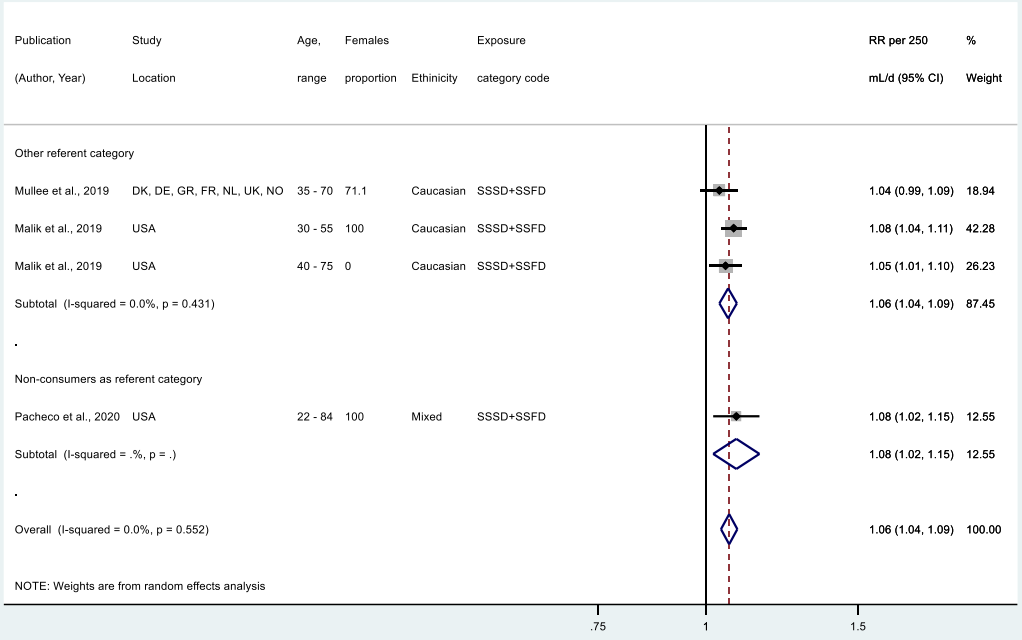


NOTE: Weights are from random effects analysis
.75
1
1.5


Sugar-sweetened beverages intake and Incidence of CVD
Linear RRs by Follow-up time (per 250 mL/day)
Publication (Author, Year)
Study Location
Age, range
Females proportion
Ethinicity
Exposure category code
RR per 250 mL/d (95% CI)
% Weight
<=20 years
Mullee et al., 2019 DK, DE, GR, FR, NL, UK, NO 35 - 70 71.1 Caucasian SSSD+SSFD 1.04 (0.99, 1.09) 18.94
Pacheco et al., 2020 USA 22 - 84 100 Mixed SSSD+SSFD 1.08 (1.02, 1.15) 12.55
Subtotal (I-squared = 19.7%, p = 0.264) 1.06 (1.01, 1.10) 31.49
.
>20 years
Malik et al., 2019 USA 30 - 55 100 Caucasian SSSD+SSFD 1.08 (1.04, 1.11) 42.28
Malik et al., 2019 USA 40 - 75 0 Caucasian SSSD+SSFD 1.05 (1.01, 1.10) 26.23
Subtotal (I-squared = 0.0%, p = 0.435) 1.07 (1.04, 1.10) 68.51
.
Overall (I-squared = 0.0%, p = 0.552) 1.06 (1.04, 1.09) 100.00
NOTE: Weights are from random effects analysis
.75
1
1.5


Sugar-sweetened beverages intake and Incidence of CVD
Linear RRs by Study location (per 250 mL/day)
Publication (Author, Year)
Study Location
Age, range
Females proportion
Ethinicity
Exposure category code
RR per 250 mL/d (95% CI)
% Weight
USA
Pacheco et al., 2020 USA 22 - 84 100 Mixed SSSD+SSFD 1.08 (1.02, 1.15) 12.55
Malik et al., 2019 USA 30 - 55 100 Caucasian SSSD+SSFD 1.08 (1.04, 1.11) 42.28
Malik et al., 2019 USA 40 - 75 0 Caucasian SSSD+SSFD 1.05 (1.01, 1.10) 26.23
Subtotal (I-squared = 0.0%, p = 0.667) 1.07 (1.04, 1.10) 81.06
.
Europe
Mullee et al., 2019 DK, DE, GR, FR, NL, UK, NO 35 - 70 71.1 Caucasian SSSD+SSFD 1.04 (0.99, 1.09) 18.94
Subtotal (I-squared = .%, p = .) 1.04 (0.99, 1.09) 18.94
.
Overall (I-squared = 0.0%, p = 0.552) 1.06 (1.04, 1.09) 100.00
NOTE: Weights are from random effects analysis
.75
1
1.5

Sugar-sweetened beverages intake and Incidence of CVD
Linear RRs by Exposure categorisation (per 250 mL/day)



Appendix E – Sensitivity analyses

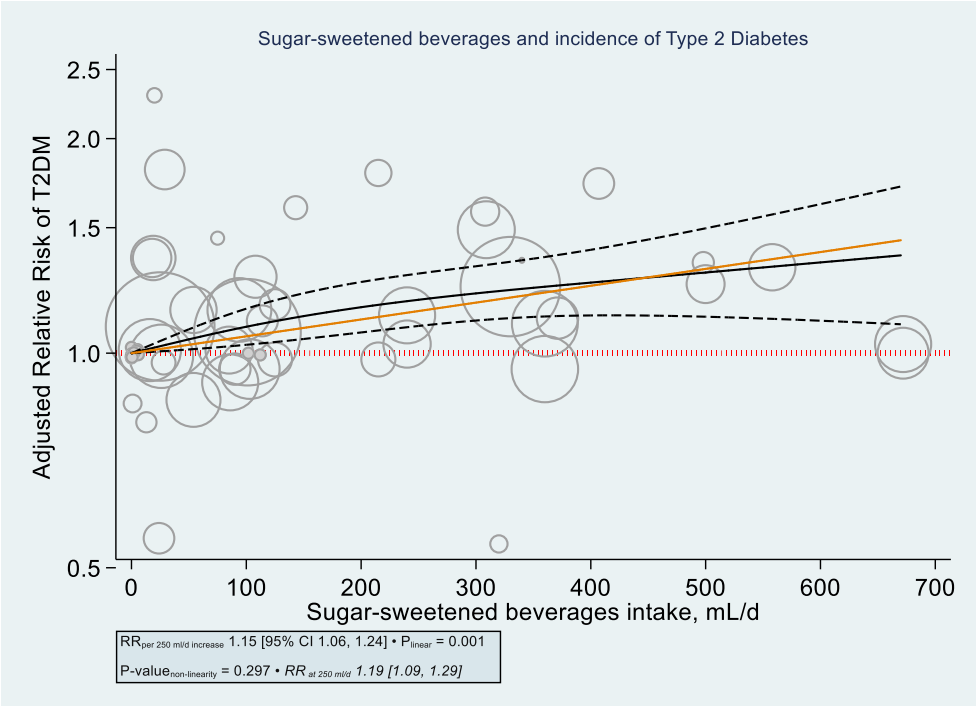


Figure E.1 SSBs and T2DM – sensitivity analysis excluding studies in tier 3 (Huang et al., 2017; Kang and Kim, 2017; Ericson et al., 2018)

Figure E.2 SSBs and T2DM – sensitivity analysis excluding a study assessing the outcome as T2DM and prediabetes (Ma et al., 2016)

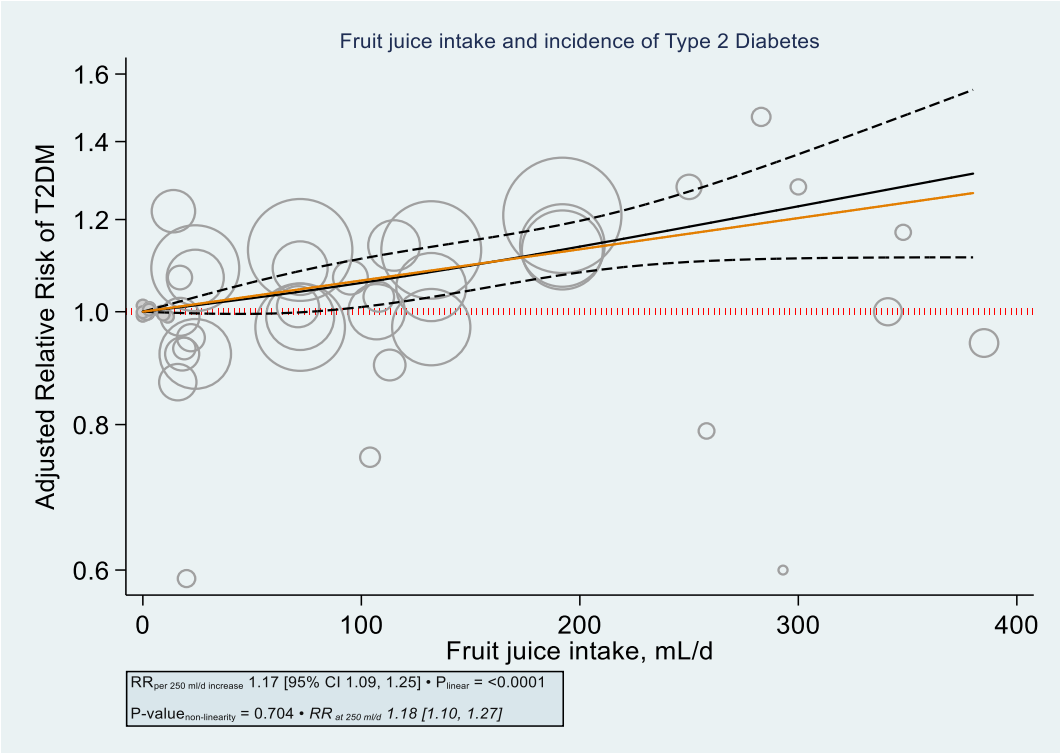


Figure E.3 FJs and T2DM – sensitivity analysis excluding studies in tier 3 (Eshak et al., 2013; females and males)

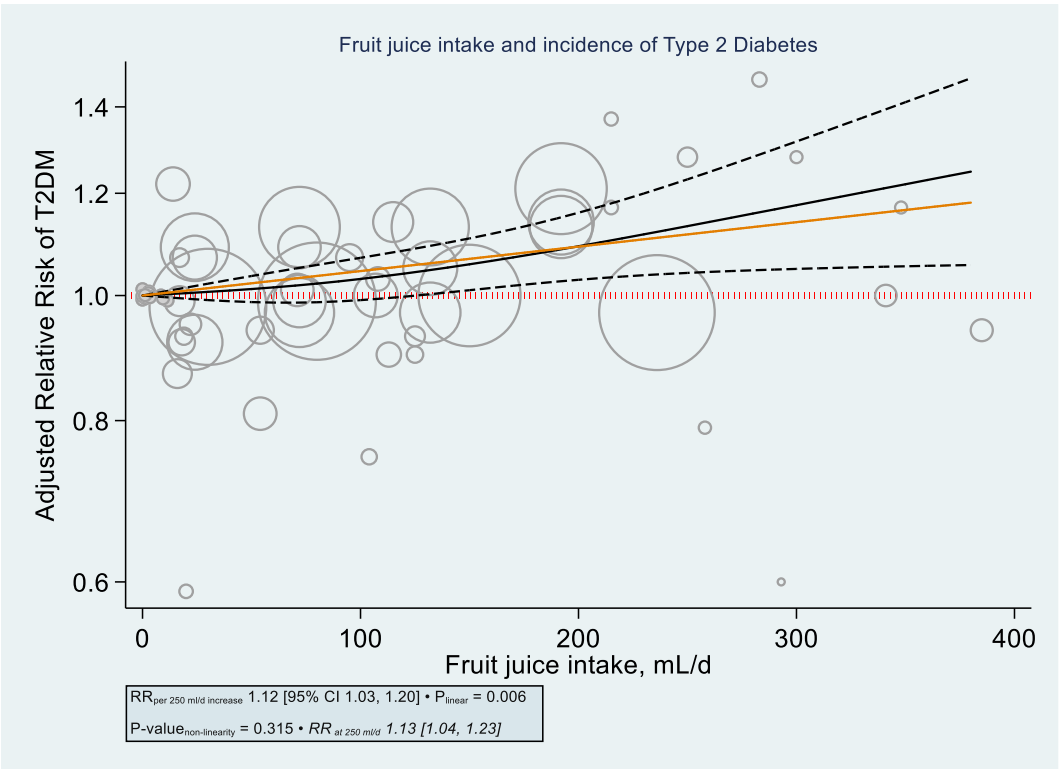


Figure E.4 FJs and T2DM – sensitivity analysis including a study that applied a different analytical approach (STD for Total Energy Intake; Auerbach et al., 2017)

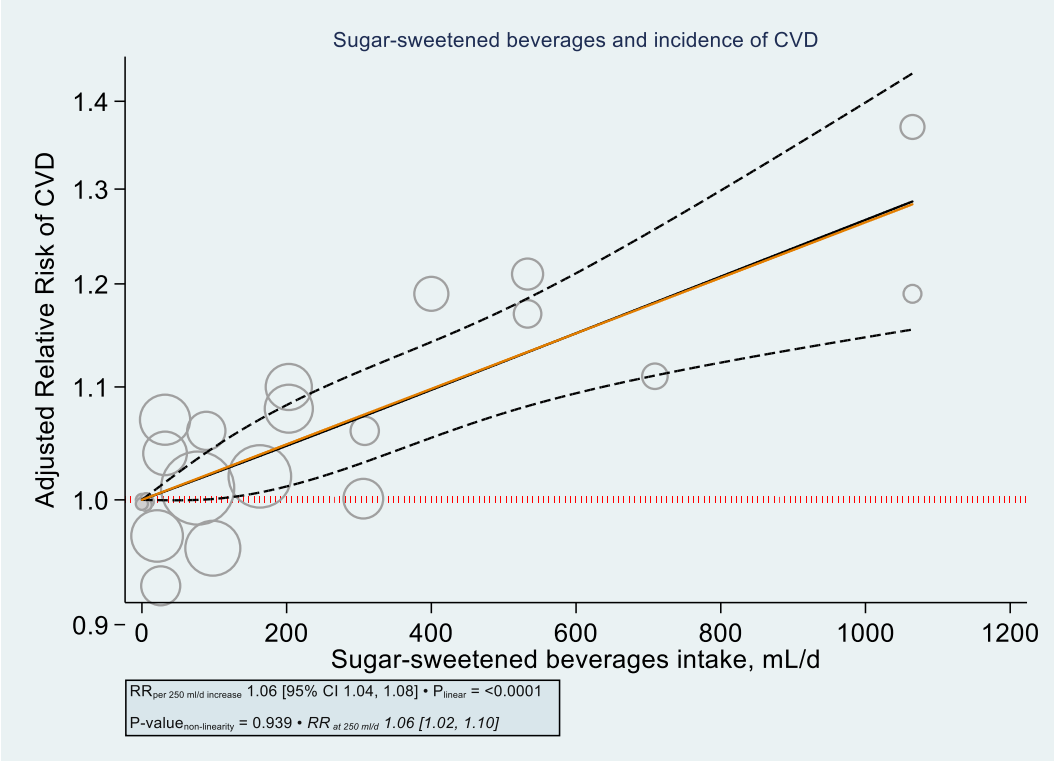


Figure E.5 SSBs and CVD – sensitivity analysis including a study that applied a different analytical approach (STD for Total Energy Intake; Sonestedt et al., 2015)

Appendix F – Funnel plots

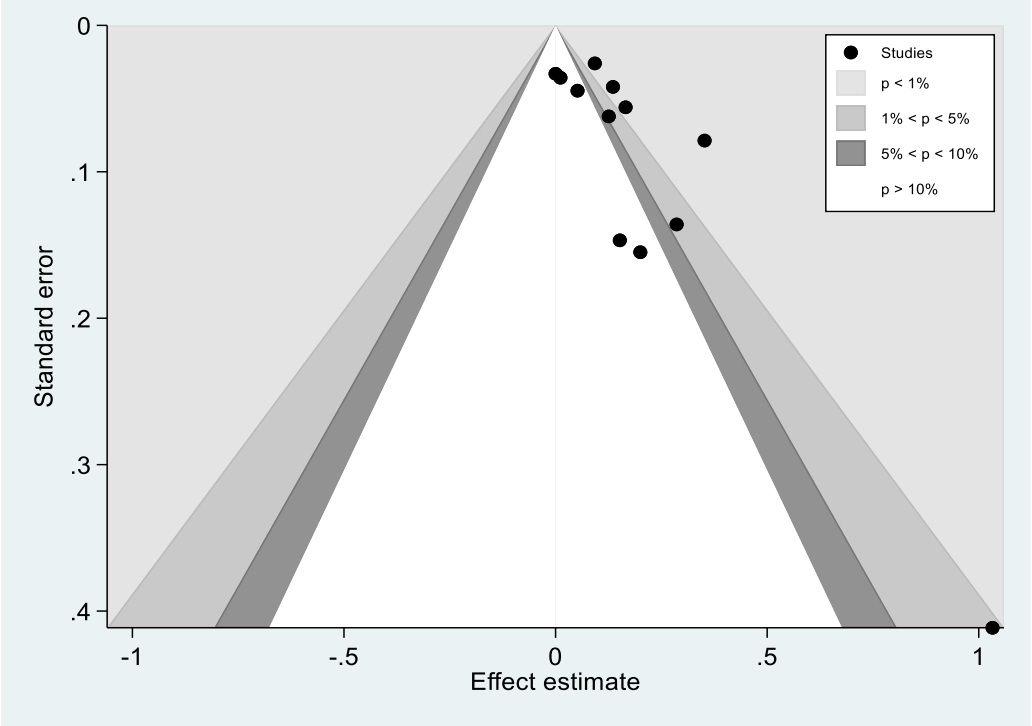


Figure F.1 Contour funnel plot of RRs effect estimates of T2DM and SSBs against their standard error and with superimposed areas of statistical significance

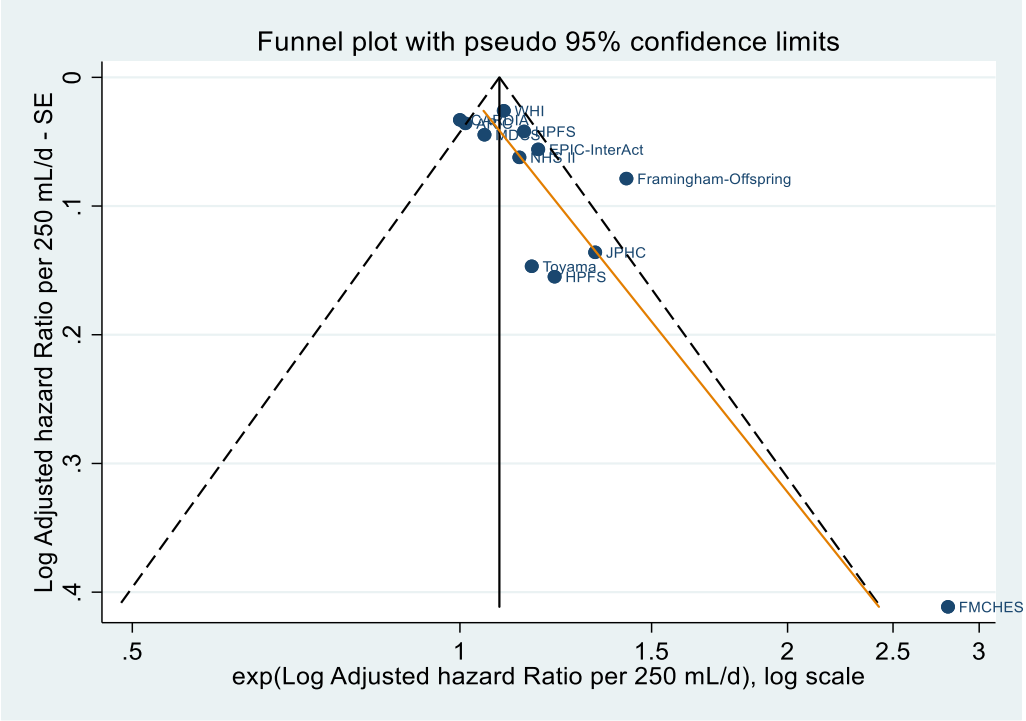


Figure F.2 Funnel plot of RRs effect estimates of T2DM and SSBs against their standard error and with Egger's regression line to test for plot asymmetry (p = 0.021)

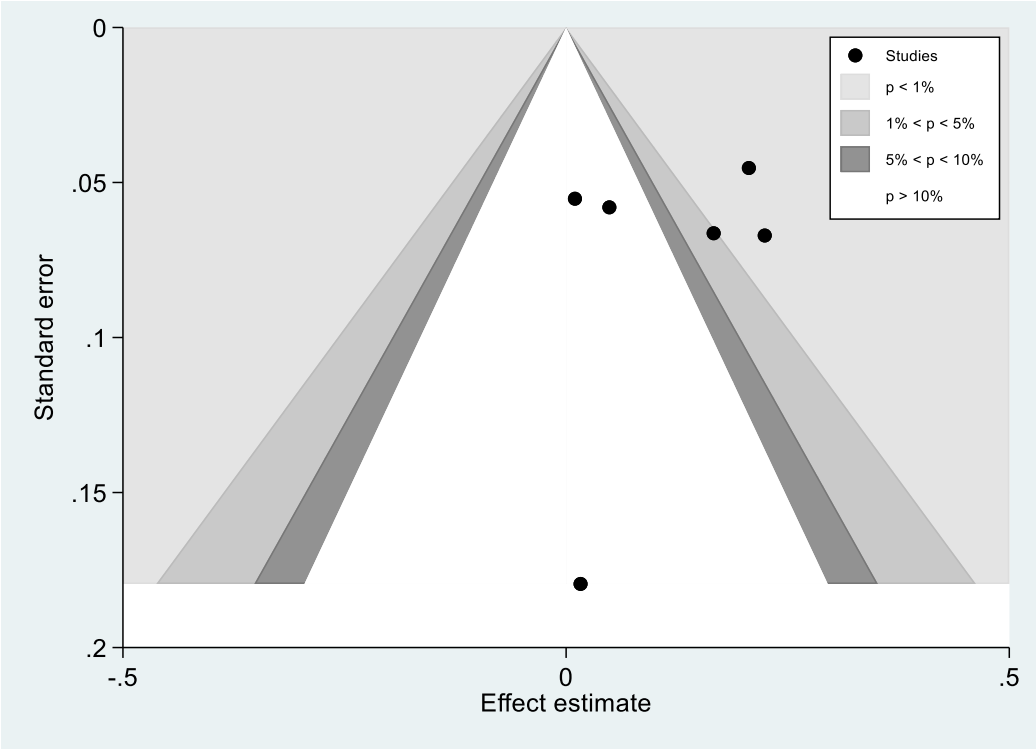


Figure F.3 Contour funnel plot of RRs effect estimates of T2DM and FJs against their standard error and with superimposed areas of statistical significance

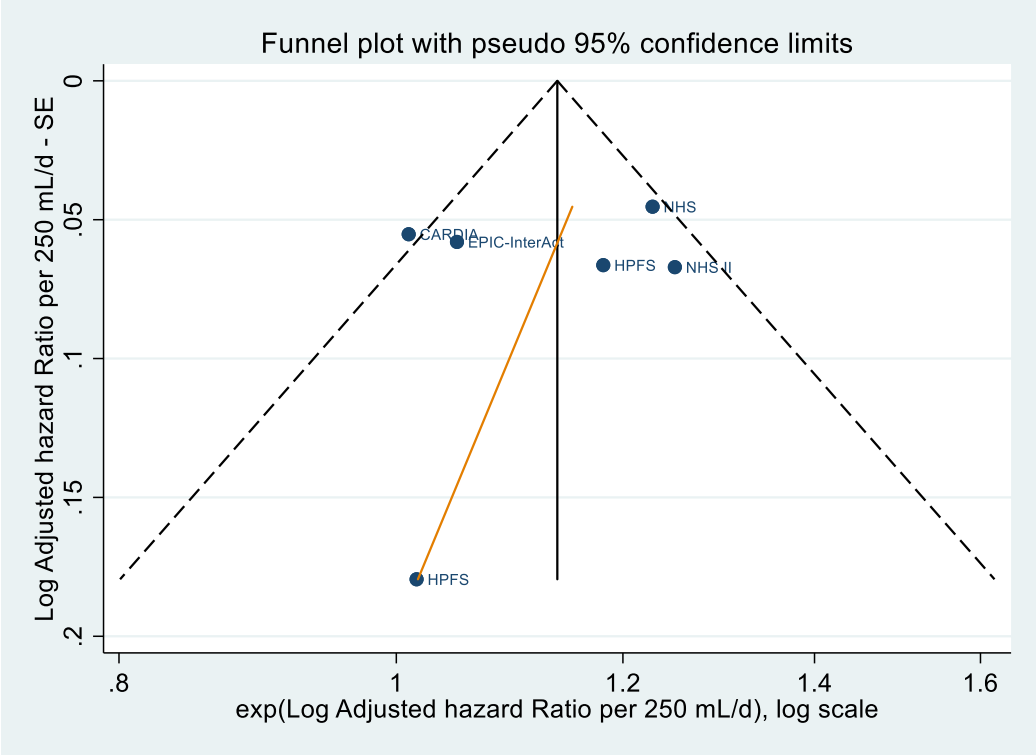


Figure F.4 Funnel plot of RRs effect estimates of T2DM and FJs against their standard error and with Egger's regression line to test for plot asymmetry (p = 0.703)

Appendix G – Predicted RRs with 95% CIs from linear and non-linear models by relevant intakes

Table G.1 Sugar-sweetened beverages and T2DM dose–response meta-analysis

Linear model				Non-linear model			
SBB, mL/d	**RR**	**CI_lb**	**CI_ub**	**SBB, mL/d**	**RR**	**CI_lb**	**CI_ub**
0	1	1	1	**0**	1	1	1
25	1.01	1.01	1.02	**25**	1.01	1	1.02
50	1.02	1.01	1.04	**50**	1.03	1.01	1.05
75	1.04	1.02	1.06	**75**	1.04	1.01	1.07
100	1.05	1.03	1.07	**100**	1.05	1.02	1.09
125	1.06	1.03	1.09	**125**	1.07	1.02	1.11
150	1.08	1.04	1.11	**150**	1.08	1.03	1.13
175	1.09	1.05	1.13	**175**	1.09	1.04	1.15
200	1.1	1.05	1.15	**200**	1.11	1.05	1.17
225	1.12	1.06	1.18	**225**	1.12	1.06	1.18
250	1.13	1.07	1.2	**250**	1.13	1.07	1.2
275	1.14	1.08	1.22	**275**	1.15	1.08	1.22
300	1.16	1.08	1.24	**300**	1.16	1.09	1.24
325	1.17	1.09	1.26	**325**	1.17	1.09	1.26
350	1.19	1.1	1.29	**350**	1.19	1.1	1.28
375	1.2	1.1	1.31	**375**	1.2	1.1	1.31
400	1.22	1.11	1.33	**400**	1.21	1.11	1.33
425	1.23	1.12	1.36	**425**	1.23	1.11	1.36
450	1.25	1.13	1.38	**450**	1.24	1.11	1.38
475	1.26	1.13	1.41	**475**	1.26	1.12	1.41
500	1.28	1.14	1.43	**500**	1.27	1.12	1.44
525	1.29	1.15	1.46	**525**	1.28	1.12	1.47
550	1.31	1.16	1.49	**550**	1.3	1.13	1.5
575	1.33	1.16	1.51	**575**	1.31	1.13	1.53
600	1.34	1.17	1.54	**600**	1.33	1.13	1.56
625	1.36	1.18	1.57	**625**	1.34	1.13	1.59
650	1.38	1.19	1.6	**650**	1.36	1.13	1.63
675	1.39	1.19	1.62	**675**	1.37	1.14	1.66
700	1.41	1.2	1.65	**700**	1.39	1.14	1.7
725	1.43	1.21	1.68	**725**	1.41	1.14	1.73
750	1.45	1.22	1.71	**750**	1.42	1.14	1.77
775	1.46	1.23	1.75	**775**	1.44	1.14	1.81
800	1.48	1.23	1.78	**800**	1.45	1.15	1.84
825	1.5	1.24	1.81	**825**	1.47	1.15	1.88
850	1.52	1.25	1.84	**850**	1.49	1.15	1.92

Table G.2 Fruit juices and T2DM dose–response meta-analysis

Linear model				Non-linear model			
FJ, mL/d	**RR**	**CI_lb**	**CI_ub**	**FJ, mL/d**	**RR**	**CI_lb**	**CI_ub**
0	1	1	1	**0**	1	1	1
25	1.02	1.01	1.02	**25**	1.01	0.99	1.03
50	1.03	1.02	1.04	**50**	1.02	0.99	1.05
75	1.05	1.03	1.07	**75**	1.03	0.99	1.08
100	1.06	1.03	1.09	**100**	1.05	1	1.1
125	1.08	1.04	1.11	**125**	1.06	1.01	1.12
150	1.09	1.05	1.14	**150**	1.08	1.03	1.14
175	1.11	1.06	1.16	**175**	1.11	1.06	1.16
200	1.13	1.07	1.19	**200**	1.13	1.08	1.19
225	1.14	1.08	1.21	**225**	1.16	1.1	1.23
250	1.16	1.09	1.24	**250**	1.19	1.11	1.28
275	1.18	1.1	1.27	**275**	1.22	1.12	1.33
300	1.2	1.11	1.29	**300**	1.25	1.13	1.39
325	1.21	1.12	1.32	**325**	1.29	1.13	1.46
350	1.23	1.13	1.35	**350**	1.32	1.14	1.53
375	1.25	1.13	1.38	**375**	1.35	1.14	1.6
400	1.27	1.14	1.41	**400**	1.39	1.15	1.67

Table G.3 Sugar-sweetened beverages and HTN dose–response meta-analysis

Linear model				Non-linear model			
SBB, mL/d	**RR**	**CI_lb**	**CI_ub**	**SBB, mL/d**	**RR**	**CI_lb**	**CI_ub**
0	1	1	1	**0**	1	1	1
25	1.01	1	1.01	**25**	1.01	1	1.02
50	1.01	1.01	1.02	**50**	1.02	1	1.04
75	1.02	1.01	1.02	**75**	1.03	1.01	1.05
100	1.02	1.01	1.03	**100**	1.04	1.01	1.07
125	1.03	1.02	1.04	**125**	1.05	1.02	1.08
150	1.04	1.02	1.05	**150**	1.05	1.02	1.08
175	1.04	1.03	1.06	**175**	1.06	1.02	1.09
200	1.05	1.03	1.07	**200**	1.06	1.03	1.1
225	1.05	1.03	1.07	**225**	1.07	1.03	1.1
250	1.06	1.04	1.08	**250**	1.07	1.04	1.11
275	1.07	1.04	1.09	**275**	1.08	1.04	1.11
300	1.07	1.04	1.1	**300**	1.08	1.05	1.12
325	1.08	1.05	1.11	**325**	1.09	1.05	1.13
350	1.08	1.05	1.12	**350**	1.09	1.06	1.14
375	1.09	1.06	1.13	**375**	1.1	1.06	1.14
400	1.1	1.06	1.14	**400**	1.11	1.06	1.15
425	1.1	1.06	1.14	**425**	1.11	1.07	1.16
450	1.11	1.07	1.15	**450**	1.12	1.07	1.17
475	1.12	1.07	1.16	**475**	1.12	1.07	1.17
500	1.12	1.08	1.17	**500**	1.13	1.08	1.18
525	1.13	1.08	1.18	**525**	1.13	1.08	1.19

550	1.14	1.08	1.19	**550**	1.14	1.08	1.2

Table G.4 Sugar-sweetened beverages and CVD dose–response meta-analysis

Linear model				**Non-linear model**			
SBB, mL/d	**RR**	**CI_lb**	**CI_ub**	**SBB, mL/d**	**RR**	**CI_lb**	**CI_ub**
0	1	1	1	**0**	1	1	1
25	1.01	1	1.01	**25**	1.01	1	1.01
50	1.01	1.01	1.02	**50**	1.01	1	1.03
75	1.02	1.01	1.03	**75**	1.02	1	1.04
100	1.03	1.02	1.03	**100**	1.03	1	1.05
125	1.03	1.02	1.04	**125**	1.03	1.01	1.06
150	1.04	1.02	1.05	**150**	1.04	1.01	1.08
175	1.04	1.03	1.06	**175**	1.05	1.01	1.09
200	1.05	1.03	1.07	**200**	1.06	1.01	1.1
225	1.06	1.04	1.08	**225**	1.06	1.01	1.12
250	1.06	1.04	1.09	**250**	1.07	1.02	1.13
275	1.07	1.04	1.1	**275**	1.08	1.02	1.14
300	1.08	1.05	1.11	**300**	1.08	1.03	1.14
325	1.08	1.05	1.11	**325**	1.09	1.03	1.15
350	1.09	1.06	1.12	**350**	1.1	1.04	1.16
375	1.1	1.06	1.13	**375**	1.1	1.05	1.16
400	1.1	1.07	1.14	**400**	1.11	1.05	1.17
425	1.11	1.07	1.15	**425**	1.12	1.06	1.17
450	1.12	1.07	1.16	**450**	1.12	1.07	1.18
475	1.12	1.08	1.17	**475**	1.13	1.07	1.18
500	1.13	1.08	1.18	**500**	1.13	1.08	1.19
525	1.14	1.09	1.19	**525**	1.14	1.09	1.2
550	1.15	1.09	1.2	**550**	1.15	1.09	1.2
575	1.15	1.1	1.21	**575**	1.15	1.1	1.21
600	1.16	1.1	1.22	**600**	1.16	1.1	1.22
625	1.17	1.11	1.23	**625**	1.17	1.1	1.23
650	1.17	1.11	1.24	**650**	1.17	1.11	1.24
675	1.18	1.11	1.25	**675**	1.18	1.11	1.25
700	1.19	1.12	1.26	**700**	1.19	1.11	1.26
725	1.2	1.12	1.27	**725**	1.19	1.11	1.28
750	1.2	1.13	1.29	**750**	1.2	1.12	1.29
775	1.21	1.13	1.3	**775**	1.21	1.12	1.3
800	1.22	1.14	1.31	**800**	1.21	1.12	1.31
825	1.23	1.14	1.32	**825**	1.22	1.12	1.33
850	1.23	1.15	1.33	**850**	1.23	1.12	1.34
900	1.25	1.15	1.35	**900**	1.24	1.12	1.37
950	1.26	1.16	1.37	**950**	1.25	1.12	1.4
1000	1.28	1.17	1.4	**1000**	1.27	1.13	1.43
1050	1.3	1.18	1.42	**1050**	1.28	1.13	1.46

Glossary, abbreviations, and acronyms

AIC	Akaike Information Criteria
BMI	Body mass index
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
FJ	Fruit juice
HTN	Hypertension
KoGES	Korean Genome and Epidemiology Study
LOWESS	Locally weighted scatterplot smoother
NCC	Nested case–control
PC	Prospective cohort
PCC	Population/Concept/Context
RCS	Restricted Cubic Splines
RoB	Risk of bias
RR	Relative risk
SSB	Sugar-sweetened beverage
STD	Standardised
T2DM	Type 2 diabetes mellitus
TLGS	Tehran Lipid and Glucose Study